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CONTENTS

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ANTECEDENTS OF INFANTILE CEREBRAL PALSY

BY

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The causes of infantile cerebral palsies, and especially of diplegia, have been much argued. Collier's (1924) able discussion of diplegia shows the inconclusiveness of many of the arguments.

Before studying particular features, it seemed reasonable to survey the histories antecedent to the development of palsy obtained in a series of cases. The term ' infantile cerebral palsy ' includes several syndromes, and these different conditions may have different causes. The series has, therefore, been grouped into sets of cases with similar clinical pictures. Only two of these, the spastic and the athetoid, form large enough groups for statistical study, and this paper is concerned mainly with them.

Owing to the different methods of classification used by various observers (Evans, 1948) only patients examined personally are included. Furthermore, children whose mothers were not questioned are excluded; fathers rarely have precise knowledge about the birth of their children. Information was also sought by written questionnaire from doctors or midwives in attendance at childbirth, or from hospitals or nursing homes where the patients were born. Replies were received from 80 per cent. of those questioned. The history was thus usually compiled from two sources. They were rarely contradictory. Where they were, the case was judged on the apparent merits of the two stories. The medical record was often more precise about pregnancy and labour, while the mother was almost always more circumstantial in her account of the condition of the newly born child.

About half the patients were seen in hospital and private practice, and the rest at the preliminary examination of children whose admission to a school for children with cerebral palsy was sought. The mothers of fifty children not suffering from disease of the central nervous system, seen in hospital and private practice, were questioned similarly. There may have been differences in social class between the children in the ' control group ' and the patients, as no control for the children seen at the school was devised. This should be taken into account in considering such factors as parental age, size of family, and use of obstetric analgesia. The groups were balanced as to age, and all were seen within the same period of about fifteen months. Their ages varied from 1 to 13 years (average 6·4 years, standard deviation 3·1). The total number of patients was 122. In eight the mother was not interviewed, and only the remaining 114 are considered here.

Classification

The clinical condition may be classified by reference to the distribution of the palsy and to its functional type.

The distribution is expressed in terms of the limbs affected as monoplegia, hemiplegia, paraplegia, triplegia, and tetraplegia. The last term is preferred to ' diplegia ' because this is sometimes unfortunately used in the same sense as ' paraplegia '.

On the functional side there have also been ambiguities, but there must be few cases which cannot be described as spastic, athetoid, flaccid, choreic, or ataxic.

The terms may be combined, theoretically in any combination, but in practice as spastic or flaccid paraplegia or tetraplegia. Athetosis, chorea and ataxia are usually generalized and only exceptionally need topical qualification. Hemiplegia is almost always spastic. Double hemiplegia may be a useful concept, and indeed two cases classified in this series as ' mixed type, spastic legs and athetoid arms ' were probably double hemiplegias. Some of the athetoid patients might also be given the same label. For reasons indicated elsewhere (Evans, 1948) I have not considered extensor plantar responses as a criterion for taking these children out of the athetoid group.

It is often difficult to distinguish between paraplegia and mild tetraplegia. I have therefore included paraplegias and tetraplegias in the same group.

The classification of the 114 patients in this series is shown in table 1. Nearly two-fifths were cases of spastic para- or tetraplegia and will be referred to simply as ' spastic '; a similar number of cases of athetoid tetraplegia or double athetosis will be referred to as ' athetoid.' Phelps's (1941) generalization that 40 per cent. of cases are spastic, 40 per cent. athetoid, and 20 per cent. ataxic is borne out only as far as the two major groups are concerned.

Known Causes

Sometimes the cause of the cerebral paralysis is known, or at least appears probable from the history. This was so in seventeen of these 114 patients.

The primary conditions appeared to be:

1. **Hydrocephalus** starting post-natally, four cases. In two of these the cause of the hydrocephalus was unknown, in two it followed meningitis. By the time the children were seen the condition did not appear to be progressing. Three of these children had spastic paraplegia. In the fourth there was athetosis, but here there was also a history of repeated asphyxial attacks during the attack of meningitis.

2. **Meningitis** without hydrocephalus, one case. This was a pneumococcal meningitis in a feeble baby suffering from congenital heart disease. Intrathecal penicillin and saline lavage to remove a spinal block were part of the treatment. This child had hemiplegia.

TABLE 1

CLINICAL CLASSIFICATION OF 114 CHILDREN SUFFERING FROM CEREBRAL PALSY

Diagnosis	No.	%
Spastic para- or tetraplegia	44	39
Flaccid para- or tetraplegia	3	3
Athetoid tetraplegia	44	39
Monoplegia	3	3
Hemiplegia	10	9
Ataxia	4	4
Chorea	1	1
Mixed types	5	4

3. **Encephalitis,** two cases. Illnesses diagnosed as polioencephalitis at ten months and measles encephalitis at four years preceded spastic tetraplegia and athetosis in these two children.

4. **Haemorrhagic disease of the newborn,** two cases. One may doubt whether intracranial haemorrhage caused the nervous lesions in these cases, but it seems unreasonable to leave them in the group, to be discussed later, in which there was no obvious cause. One child had left hemiplegia with right optic atrophy. In the other child haemorrhagic disease was associated with severe asphyxia; generalized athetosis later became apparent.

5. **Erythroblastosis foetalis,** eight cases. The association between Rhesus-group incompatibility and kernicterus is well known. In these cases the diagnosis was made in the neonatal period and was confirmed retrospectively. In two the mother's blood was not investigated. Each of the other six was Rhesus-negative. In three the indirect Coombs-Mourant-Race test was also done. It was positive in two. In one a year had elapsed since the birth of the affected child. The other was five years old; but the mother had had another baby, suffering from icterus gravis, one month before the test was done. In the third case the test was negative but six years had passed since the last (and affected) child was born.

The neurological condition in four of these children was athetoid, and in one choreic; one was classified as ataxia. The other two were atonic and tetraplegic, but they were only a year old and the ultimate diagnosis is doubtful.

One must consider the possibility that, in other cases in which erythroblastosis was not diagnosed, Rhesus-incompatibility may have been the cause of the palsy. Bakwin and Wiener's (1947) investigation of the blood groups of twenty-three athetoid children and their mothers makes this hypothesis seem unlikely to be true.

Dr. I. A. B. Cathie kindly carried out indirect Coombs-Mourant-Race tests on thirty-eight of the mothers of palsied children who had not had icterus gravis, selected because they lived in London. The result was negative in every case. In twenty-eight of them Rhesus grouping was also done; twenty-six were Rh-positive. The affected children of the two Rh-negative mothers were first-born. One may conclude that occult Rhesus incompatibility is not a common cause of cerebral palsy.

CONCLUSIONS: KNOWN CAUSES OF CEREBRAL PALSY

1. Hydrocephalus, severe meningitis, encephalitis, and possibly intracranial haemorrhage due to haemorrhagic disease of the newborn appeared occasionally in this group as causes of cerebral palsy.

2. Erythroblastosis foetalis due to Rhesus incompatibility is about as common as all the other known causes put together.

3. Altogether, these ' known causes ' accounted for the disease in only 15 per cent. of the patients.

Family History

The rest of this paper is (except where otherwise stated) concerned only with the cases due to ' unknown causes,' and of them only with cases of spastic para- or tetraplegia and of athetosis. Each of these two groups contained thirty-eight patients.

' Hereditary spastic paraplegia appears to be extremely rare in this country ' (Bell and Carmichael, 1939). In the whole series of 114 cases there was no history of infantile cerebral palsy in the grandparents, parents, uncles, or aunts of the patients. One microcephalic hemiplegic boy had a microcephalic tetraplegic brother. The other members of the families were not examined for evidence of incipient or slight paralysis, but it appears that heredity is not commonly an important influence in producing the disease.

Consanguinity of the parents was discovered in one case of spastic paraplegia and in one of the control

cases. This case of spastic paraplegia also provided the only example of a developmental anomaly unrelated to the nervous system or special senses: the child had only four lumbar vertebrae.

Two siblings of patients had developmental anomalies: a cranial deficiency of some sort in one case, and spina bifida and mental defect in another. Two siblings of control children may have had congenital anomalies, congenital heart disease in one case and epilepsy with mental defect and a big head in the other.

Sex. A surprising number of athetoid children were boys (table 2), but this may have been a chance finding.*

TABLE 2
SEX OF PATIENTS

Sex	Spastic 38	Athetoid 38	Control 50
Male ..	19	24	26
Female ..	19	15	24

TABLE 3
AGE OF PARENTS AT TIME OF BIRTH OF AFFECTED CHILD

Group	Age of father		Age of mother	
	Average	S.D.	Average	S.D.
Spastic 38 ..	34	5·6	31	5·0
Athetoid 38 ..	33	5·1	30	4·9
Control 50 ..	32	6·8	31	4·9

TABLE 4.
NUMBER OF PREGNANCIES AND NUMBER OF LIVE BIRTHS IN MOTHERS OF SPASTIC, ATHETOID, AND CONTROL PATIENTS

	Spastic 38		Athetoid 38		Control 50	
	Total	Average	Total	Average	Total	Average
Pregnancies ..	91	2·4	85	2·2	130	2·6
Live births ..	80	2·1	70	1·8	123	2·5

Parental age (table 3). The age of the parents was similar in the three comparable groups of spastic, athetoid, and control children.

Pregnancies and live births. The average numbers of times the mother had been pregnant at the time of observation are shown in table 4. The differences between the three groups are slight, and as this factor is much affected by social status it would be unwise to pay attention to them.

* I am indebted to Dr. P. E. Polani for the statistical treatment of the information in tables 2, 4, 5, 7, 8, 10, and 11. The χ^2 test was used as the main test of significance. It was assumed that values of P (probability) of less than 0·05 were not likely to have arisen by chance. The standard error of the difference between proportions was considered not likely to be significant if it exceeded twice the standard error.

TABLE 5
ONLY CHILDREN AND SINGLE PREGNANCIES

Group	Only surviving child		Only one pregnancy	
	No.	%	No.	%
Spastic 38 ..	14	36	13	34
Athetoid 38 ..	14	36	11	29
Control 50 ..	12	24	10	20

The number of live children produced in relation to the number of pregnancies is less affected by this consideration, and comparisons of the athetoid and control figures ($P = <0·01$) indicates that there may at times be a lethal agent affecting the foetus in families producing athetoid children. The differences between athetoid and spastic ($P = 0·5$) and spastic and control ($P = >0·1$) are less impressive.

One-child sterility (table 5). One might expect to find a high proportion of only children in the affected families, because these children need much maternal care, or possibly even because of some lack of fecundity. These conditions are affected by social state, and the differences shown in this series are inconsiderable.

Abortions (table 6). The number of abortions in the families of the patients did not differ significantly from that in the control families.

Birth rank (position in family) (table 7). The position of the affected child in the family, expressed as the number of the pregnancy which produced him, and not as his place among surviving children, is shown in table 7. The difference between the number of first-born children in spastic and control groups may well be due to chance, but the difference between athetoid and control is very unlikely to be fortuitous.

Of athetoid children 79 per cent. were firstborn, of controls only 44 per cent. The mother of an athetoid child is unlikely to have a healthy child before she has one who develops athetosis, except in the special case of kernicterus. She actually did so in only four of the thirty-eight instances in this

TABLE 6
NUMBER OF ABORTIONS IN SPASTIC, ATHETOID, AND CONTROL PATIENTS

Group	Abortions			
	Before patient's birth	After patient's birth	Total	%
Spastic 38	6	4	10	26
Athetoid 38 ..	2	7	9	23
Control 50 ..	3	5	8	16

TABLE 7
BIRTH RANK

Number of pregnancy	Spastic		Athetoid		Control	
	No.	%*	No.	%	No.	%
1	21	56	30	80	22	44
2	4	11	5	13	13	26
3	7	19	1	3	11	22
4	2	5	2	5	1	2
5	3	8	0		1	2
6	0		0		1	2
7	0		0		1	2
Unknown	1		0		0	
Total ..	38		38		50	

* Of thirty-seven cases.

series, for in the eight cases in which the child was not the result of the first pregnancy abortions preceded the birth of the affected child in two, one child died twenty-four hours after birth, and another has spina bifida (treated surgically) and mental defect.

Twinning. It is noteworthy that six of these seventy-six cases of cerebral palsy of obscure etiology were twins (table 8), while there were no examples of twins in the fifty controls or their siblings, or in the siblings of the affected children. The numbers are small and may have occurred by chance, but the proportion, particularly in spastics, suggests the need for study in a larger group. Bakwin and Wiener (1947) note twin births in three of twenty-three cases of athetosis.

The twin siblings of the two athetoid patients were healthy, but, of the four twin siblings of spastics, two were stillborn macerated foetuses, and one died on the first day of life, while the fourth was healthy.

CONCLUSIONS: FAMILY HISTORY

1. The following factors appear not to be commonly associated with the production of spastic or athetoid cerebral palsy: a family history of the disease; parental consanguinity; parental age.
2. Birth-order is unimportant in spastic children.
3. Other factors which were not demonstrated in this survey to be associated with the production of spastic or athetoid palsy, although there was some suggestion from the figures that they might be worth more extended investigation were: the mother having no pregnancies apart from that producing the affected child; the number of abortions; twinning in association with the disease.
4. The mothers of spastic patients had rather few living children, but this was not shown to be significant.
5. The following factors appeared to be associated with the production of athetoid palsy: primogeniture; the rather small number of living children born to the mothers of these children.

TABLE 8.
TWINS

Group	No. of twin births	Patient was		Other twin was		Ovularity	
		1st	2nd	Stillborn or died on first day	healthy	bin–	unknown
Spastic 38	4	3	1	3	1	1	3
Athetoid 38	2	1	1	0	2	0	2
Control 50	0	—	—	—	—	—	—

TABLE 9
ILL HEALTH DURING PREGNANCY

Condition	Spastic 38	Athetoid 38	Control 50
Threatened abortion	3	5	4
Albuminuria alone	1	2	0
Toxaemia	1	2	2
Prolonged vomiting	1	4	2
Pyelitis	0	0	2
Etc.	3	1	2
Total diseases ..	9	14	12
Total mothers affected ..	9	11	10

Health During Pregnancy

In view of the frequency of premature birth in the palsied group it is rather surprising to find that there was no strikingly increased incidence of ill-health

TABLE 10
BIRTH WEIGHTS

Weight lb. and oz.	Kg.	Spastic 38	Athetoid 38	Control 50
<1-8	<0·7	1	0	0
1-9 to 2-8	0·8–1·2	2	2	0
2-9 to 3-8	1·3–1·6	2	3	0
3-9 to 4-8	1·7–2·0	9	2	1
4-9 to 5-8	2·1–2·5	4	5	3
5-9 to 6-8	2·6–2·9	6	7	7
6-9 to 7-8	3·0–3·4	9	12	14
7-9 to 8-8	3·5–3·8	3	3	10
8-9 to 9-8	3·9–4·3	0	2	8
9-9 to 10-8	4·4–4·8	1	0	0
>10-8	>4·8	1	0	0
Unknown but mature		0	1	2
Unknown but premature		1	0	0
Average ..		5 lb. 6 oz.	6 lb. 0 oz.	7 lb. 8 oz.
S.D.		2·04	1·87	1·46

during pregnancy in the mothers of affected children (table 9).

Immaturity (Birth Weight)

Because of the uncertainty of estimates of the duration of pregnancy the birth weight was adopted as a measure of immaturity. A baby weighing 5½ lb. (2,500 g.) or less was considered to be immature (table 10). The number of them in the control group was proportionate to that in the general population (Crosse, 1945). There is a significant increase in the number of premature infants among the patients compared with the controls. This is especially noticeable in the spastic group, but the difference between spastic and athetoid may be due to chance. So may the double peak in the distribution of birth weights of the spastic children.

Labour

In table 11 are shown some of the conditions occurring at parturition. Information about them is inprecise in some (for example, duration of labour) and precise in others (for example, instrumental

TABLE 11
COMPLICATIONS OF LABOUR

	Spastic 38	Athetoid 38	Control 50
Premedication known ..	3	6	4
Anaesthesia or analgesia ..	17 (45%)	33 (87%)	19 (38%)
Forceps	6 (16%)	15 (40%)	5 (10%)
Caesarean section ..	0	1	0
Presentation—vertex	36	37	47
breech	2	2	2
face ..	0	0	1
Placenta praevia ..	1	2	0
Inertia	0	1	0
Prolapsed cord ..	0	2	0
'Dry labour' ..	0	1	0
Eclampsia	1	0	0
Labour : precipitate ..	3	2	3
lasting more than 12 hours	13	14	12

delivery), but there seems to be little difference between the three groups except with respect to the use of anaesthetics and of forceps, which was much more frequent at the births of athetoid children than in the other cases.

Neonatal Condition

For a description of the neonatal condition it was usually necessary to depend on the mothers' accounts. Specific enquiries were made about blue and white asphyxia, efforts at resuscitation, inefficiency in sucking or convulsions in the first two weeks of life, birth palsy, and external signs of injury (table 12). Resuscitation need not be considered separately from asphyxia, and the figures for blue and white asphyxia have been combined.

There is a great difference in the incidence of neonatal asphyxia in the athetoid and the control groups. Asphyxia was in most cases prolonged, for example, 'blue for twenty-four hours,' 'atelectasis and cerebral symptoms for three weeks, not expected to live,' 'dead two and a half hours, then she moved so the doctor sent her to hospital,' 'white asphyxia for twenty-four hours, in oxygen tent five days,' 'strung up by the feet for forty-eight hours as she'd so much in her lungs she couldn't breathe,' 'breathing two or three times a minute for a long time.' In four cases there was apparently no early asphyxia, but a history of attacks of collapse and cyanosis starting between the third and the tenth day.

There was only one athetoid case without a history of asphyxia. He was the fourth child of healthy Rh-positive parents. The first two children were healthy, the third was said to be jaundiced at birth but the jaundice soon faded. The patient, the fourth child, was also jaundiced at birth, and although he was born at full term and weighed eight pounds he was thought to have remained yellow for about four months. If he is really an

TABLE 12
NEONATAL CONDITIONS (FIGURES IN BRACKETS REFER TO MATURE CHILDREN ONLY)

Feature	Spastic 38 (20)	Athetoid 38 (28)	Control 50 (48)
Asphyxia	8 (3)	37 (27)	0 (0)
Resuscitation ..	5 (1)	16 (13)	0 (0)
Inefficient sucking	14 (6)	30 (23)	3 (3)
Convulsions ..	2 (1)	8 (5)	0 (0)
External injury ..	1 (0)	6 (5)	0 (0)
Palsy (facial or brachial) ..	2 (0)	2 (2)	0 (0)

example of the effects of kernicterus, then one may say that every athetoid child had suffered from icterus gravis neonatorum or asphyxia, except in the case in which there was a history of measles encephalitis.

The difference in the incidence of asphyxia in these two groups is apparent even if premature babies are omitted. This is true also for difficulty in sucking, convulsions, and external signs of injury.

When spastic and control are compared we find a significantly increased incidence of asphyxia and difficulty in sucking, but this is not evident if premature babies are excluded. Convulsions and injury were uncommon in the spastic cases.

Comparing spastic and athetoid infants, there is a significantly increased incidence among the latter of

asphyxia and of inefficiency in sucking. This conclusion is unaffected by exclusion of the premature infants. The difference in incidence of convulsions and of external injury was probably not significant.

Discussion

The histories of these patients were surveyed in the hope that profitable lines for further investigation might be discovered. A detailed review of the etiology and pathology of cerebral palsy would be out of place here, but some conceptions of the subject may be mentioned.

Little noted in 1843, and stressed in 1862, the coincidence of 'abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum' with cerebral palsy. McNutt attached importance to meningeal haemorrhage, Brissaud to prematurity. These early concepts were severely criticized by Freud (1897) and Collier (1899, 1924), who considered that agenesis of cerebral neurones, caused by some unknown noxious influence which was only exceptionally hereditary, was the essential lesion. Collier's views have been widely accepted in this country, but it should be noted that he was investigating 'cerebral diplegia.' Little was discussing a variety of 'deformities.' Classification is difficult owing to changes in terminology, but if we consider (for example) the incidence of neonatal asphyxia in Little's cases, we find that it occurred in: seven of sixteen cases of symmetrical spastic paralysis (cerebral diplegia and paraplegia); eight of nine cases of asymmetrical spastic paralysis (? double hemiplegia); every one of eight cases of hemiplegia; every one of seven cases with irregular movements, probably athetoid. Collier's conclusions apply to cerebral diplegia, but are often referred to cerebral palsy in general.

It seems reasonable to try to classify the various types of cerebral palsy and to investigate their etiology separately. Phelps (1938) suggests that spastic paralysis is produced by cortical damage 'which most frequently results from malplaced or too tightly placed forceps,' and athetosis by injury to the base of the brain 'as a result of too strong traction and stretching of the neck.' While approving the division one cannot applaud the conclusion about spastic paralysis, in which the forceps rate was only 16 per cent. in my cases (table 11). Brockway's (1936) division by distribution of paralysis does not appear to be helpful, but McGovern and Yannet's (1947) consideration of mentally defective adult patients shows that primogeniture and abnormal delivery are associated with asymmetrical cerebral palsy, and not with symmetrical diplegia and paraplegia. Wyllie (1943) is convinced, as a result of twenty years' observation, that the percentage of abnormal and difficult births is much greater in cases of bilateral hemiplegia, often with athetosis, than in those of spastic tetraplegia.

The series recorded here provided two groups large enough for comparison, one consisting of more or less symmetrical paraplegias and tetraplegias, the other of cases of double athetosis.

The spastic cases were associated with hydrocephalus and encephalitis, but much more often no cause of the condition was apparent. Family history, sex, parental age, birth order, parental fertility, and liability to abortion were not shown to be significant. Similarly there was no important increase in ill-health during pregnancy or in abnormalities of labour. Immaturity on the other hand was extremely common, and probably caused the feeding difficulties and asphyxial troubles which often occurred in the neonatal period. Immaturity is much commoner in these cases than in the athetoid group or in children with congenital malformations in general (Murphy, 1947), and demands investigation. For the moment we must accept Collier's (1924) poetico-pathological concept of 'the garden in early spring well sown with seeds —the neuroblasts' subject to a 'noxious influence —a sudden frost for example,' but alas only for example as we are unaware of its nature

The problem of the genesis of double athetosis holds better promise of solution. Here again family history, parental age, and history of ill-health in pregnancy are negligible, while data on sex incidence, fertility, and abortion are inconclusive. There are, however, indications that damage produced by difficult labour is significant in some way. Primogeniture and the use of anaesthesia and the forceps were common in this group, while a history of asphyxia constantly occurred in the cases not characterized by neonatal jaundice. Bakwin and Wiener (1947) made similar observations. Asphyxia produces cerebral damage but may, of course, itself be the result of intracranial injury. Further study of the mechanisms at work is likely to be fruitful. Various investigators (for example Courville, 1936; Thorner and Lewy, 1940) have demonstrated that asphyxia produces 'areas of devastation' in the brain, but it is far from certain that this is the operative process in these cases. Denny-Brown's (1946) conclusion about the genesis of status marmoratus, that: 'Its relationship to asphyxia neonatorum, as maintained by the Vogts, is as untenable as the supposed causal relationship between asphyxia and Little's disease,' is the latest but not the last word on the subject.

Summary

1. In 114 cases of cerebral palsy the history was obtained from the mother. Further information was obtained in 80 per cent. from the mother's attendant at the birth of the affected child.

2. The causes of the condition in seventeen cases appeared to be hydrocephalus (four), meningitis (one), non-suppurative encephalitis (two), possibly haemorrhagic disease of the newborn (two), and nuclear damage due to erythroblastosis foetalis (eight).

3. The remaining ninety-seven cases included thirty-eight of spastic paraplegia or tetraplegia and thirty-eight of double athetosis.

4. In the thirty-eight spastic cases a family history of the disease, parental consanguinity, sex, parental age, birth order, maternal health during pregnancy, and abnormalities of labour did not appear to be important. There was no indisputable evidence of infertility, frequent abortion, or frequent twinning in the parents of these children. Premature birth was very common in these cases.

5. In the thirty-eight athetoid cases a family history of the disease, parental consanguinity, parental age, and maternal health during pregnancy did not appear to be important.

No clear evidence was obtained of an increased incidence in males, parental infertility, unusually frequent abortion, or twinning.

In these athetoid cases primogeniture was common and the mothers had rather few living children. Prematurity was unusually common, but not to the same degree as in spastic cases. Obstetric analgesia, forceps deliveries, neonatal asphyxia, convulsions, and difficulty in feeding were common. Taken together, these features suggest an association between difficult labour and the development of double athetosis.

The conditions encountered in this survey suggest three particular lines of approach to comprehension of the genesis of cerebral palsy:

1. Close clinical and pathological investigation of individual types of cerebral palsy, rather than of 'Little's Disease' in general.

2. Elucidation of the mechanism of damage to the nervous system in conditions in which the cause is known, for example hydrocephalus, Rhesus incompatibility.

3. Experimental work on the effect of asphyxia, and of venous and arterial lesions, on the immature central nervous system.

I am deeply grateful to many doctors and midwives who answered my questionnaire; to Dr. E. B. Dawe for collecting specimens of blood and to Dr. I. A. B. Cathie for testing them; to Dr. P. E. Polani for statistical help; to the Board of St. Margaret's School, Croydon, where many of the patients were seen; and to the Trustees of the National Birthday Trust Fund for paying the expenses of the investigation.

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FOLIC ACID IN COELIAC DISEASE

A STUDY OF ITS ADMINISTRATION IN TWENTY-TWO CASES

BY

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Introduction

Folic acid, as a component of the vitamin B complex, has been recognized for many years as an essential food factor. Crude preparations of it were shown to have a haemopoietic effect in some animals. Deficiency of it was followed by depression of the formation of red cells, white cells, and platelets. In 1945 Angier et al. (1945) synthesized pure folic acid. Spies (1945) and his co-workers were the first to report the haemopoietic properties of folic acid in man. Clinical trials by Berry and Spies (1946), Zuelzer and Ogden (1946), Lopez et al. (1946), Doan (1946), Wilkinson et al. (1946), and Davidson and Girdwood (1946, 1947 a, b) followed. These proved that the administrations of synthetic folic acid was followed by a haemopoietic response similar to that produced by adequate liver therapy in some types of megaloblastic anaemia, including pernicious anaemia and the anaemias associated with sprue, pellagra, pregnancy, infancy, and malnutrition, but that there was no such response in cases of iron-deficiency anaemia, hypoplastic and aplastic anaemia, or leukaemia.

In cases of sprue, folic acid administration was shown by Spies et al. (1946) and by Davidson and Girdwood (1947 b) to be followed by improvement in intestinal function as demonstrated by the disappearance both of an abnormal radiological picture and of gastro-intestinal symptoms. Mucosal oedema, intestinal segmentation, spasm, dilatation and hypomotility were no longer present, and control of the diarrhoea and resolution of oral lesions were accompanied by gain in weight. Davidson found that intestinal function was improved after five days' administration of folic acid and before any improvement in the blood picture took place.

In three cases of coeliac disease Davidson et al. (1947 b) observed no beneficial effects following folic acid administration. The anaemia, which was hypochromic in all three cases, did not improve. The sternal marrow was examined in two of the cases and proved to be normoblastic. Weight did not increase, and diarrhoea was not relieved.

The treatment of a single case of coeliac disease by folic acid was described by Brody and Gore (1946). In their case improvement in the character of the faeces and in the general condition, and increase in weight followed the administration of folic acid. Hypochromic anaemia was present before treatment. No detailed blood findings following treatment were stated.

Dalton et al. (1946) reported the administration of folic acid in doses of 5 mg. daily to two cases of coeliac disease with megaloblastic changes in their sternal marrow. In these cases reticulocyte responses of over 25 per cent. were accompanied by striking clinical improvement.

May (1947) treated five cases of coeliac disease with folic acid intramuscularly in large doses. None of his patients had macrocytic anaemia or megaloblastic arrest in the bone marrow, and none showed any beneficial effect of the folic acid, the stools remaining unchanged, the weight stationary, and the anaemia, which was of microcytic hypochromic type, unaltered.

Investigation

In this series twenty-nine cases of steatorrhoea in infancy and childhood were selected for the exhibition of folic acid. In each case the following investigations were carried out whenever possible:

Detailed clinical history and physical examination on which an attempt was made to assess the severity of the condition.

Faecal fat analysis by a modification of Holt, Courtney, and Fales' method (vide Harrison, 'Chemical Clinical Methods,' p. 490) using a single extraction with ethyl ether.

In all cases 25 to 30 g. of fat were ingested daily for three days, and the faeces passed during this period were 'marked' by charcoal biscuits. In some of the cases the faeces were bulked and weighed and an aliquot portion analysed, an

approximate estimate being so obtained of the percentage of ingested fat excreted during the period and so of the total fat balance. In a greater number of cases bulking was not possible and a sample of faeces during the period was analysed without any attempt being made to estimate the total fat excreted.

Trypsin and lipase content of duodenal juice. In eleven cases trypsin was estimated by the casein digestion method of Gross. In three the gelatin digestion method was used. In many cases three or four attempts to withdraw duodenal juice were unsuccessful. Lipase was estimated by the ethyl butyrate breakdown method.

Fractional test meal, the Boas' gruel meal being used to estimate free and combined acid.

Oral glucose tolerance test, followed the ingestion of 0·7 to 1·5 g. of glucose per kg. of body weight, the blood glucose being estimated by Folin and Wu's method.

Blood plasma protein by Van Slyke's method; serum calcium by Kramer and Tisdell's method; inorganic phosphate by Briggs' method; and alkaline phosphatase by King and Armstrong's method.

Blood haemoglobin by Haldane's method (13·8 g. per 100 ml. = 100 per cent.); red and white cell counts.

Sternal marrow puncture.

Radiography of the alimentary tract following a barium meal; of the skeleton for evidence of osteoporosis, rickets, and delayed ossification, and of the lungs for evidence of fibrosis.

Treatment with a low-fat–high-protein diet, oral and parenteral liver extract, and vitamins was then begun in those cases not already receiving it before investigations, and during a period of one or more months the rate of gain in weight and the naked-eye character of the faeces were observed and, in some cases, further blood haemoglobin estimations were done.

Folic acid in doses of 20 mg. or 10 mg. daily was then added to the treatment for one or two months while similar observations of the weight, faeces, and haemoglobin were made.

It was considered that the rate of gain in weight and the character of the faeces were the most reliable criteria of the progress of the patient, and that a comparison of these in the same patients during periods of folic acid administration and of withholding folic acid would demonstrate any uniform effect of the folic acid better than the use of half the cases as controls.

Of the twenty-nine cases, seven were excluded from the series owing to: failure to confirm the steatorrhoea by chemical analysis of the faeces before the exhibition of folic acid in four; the general condition of the patient being too good at the time of the investigation in one; the general condition being too bad both before and during folic acid administration and death occurring just after its completion in one; and the presence of calcified abdominal glands in one.

In none of the remaining twenty-two cases was there conclusive evidence of fibrocystic disease of the pancreas. In six, examination of the duodenal juice revealed trypsin in amounts falling within the accepted normal figures—25 to 50 ml. of N/10 sodium hydroxide. In five cases less than 25 ml. were found; in three, trypsin was shown to be present but was not estimated quantitatively; and in the majority of the remainder several attempts to obtain duodenal juice failed. Radiological evidence of pulmonary fibrosis was, however, present in only one case, and in this patient the figure for trypsin was 50 ml. of N/10 sodium hydroxide. For the purposes of this clinical trial, therefore, all the patients were regarded as suffering from coeliac disease.

Summary of Clinical and Laboratory Findings

Age. The average age at the onset of symptoms was 19·8 months, the earliest 3 months, and the latest 5 years.

Sex. There were thirteen girls (59·1 per cent.) and nine boys (40·9 per cent.).

Familial incidence. There was a history of coeliac disease in the families of three of the patients (13·6 per cent.). Two of the cases were brothers, and one had a brother with coeliac disease. Also, one had a younger sister who had had steatorrhoea which had been transient.

Duration of the disease. At the time of the investigation and treatment the duration had varied from one month to six and a half years, the average being 22·5 months.

Severity of the condition. There was a considerable variation from case to case in this also: one mild case, in whom steatorrhoea was unaccompanied by any other definite disability; ten moderate cases, in whom there was also definite wasting, abdominal distension, and anorexia, but who were not seriously ill or grossly dwarfed; and eleven severe cases who manifested marked dehydration, wasting, and diarrhoea sufficient to render them dangerously ill or markedly dwarfed.

Faecal fat analysis. The results of the faecal fat analysis are shown in Table 1.

It will be seen that in the ten cases in which it was estimated the total fat excreted during the fat balance period was calculated as ranging from 14·0 per cent. to 98·0 per cent. These figures were only approximations, and 98·0 per cent. was obviously an excessive approximation. The total fat percentage by weight of dried faeces ranged from 27·3 per cent. to 69·0 per cent., the percentage of this fat which was split ranging from 60·3 per cent. to 92·5 per cent. and unsplit from 7·5 per cent. to 48·0 per cent.

Duodenal juice. Duodenal juice was obtained in only fourteen cases. In all of these trypsin was demonstrated. The amount of trypsin was estimated in eleven and the number of ml. of 0·1 per cent. casein solution completely digested by 1 ml.

TABLE 1
RESULTS OF FAECAL FAT ANALYSIS

Case		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Fat balance (percentage of ingested fat excreted)		16·0	38·6	14·0	33·0	15·0								46·6			97·0		14·0		98·0	39·0	
Total fat (percentage of faeces by dried weight)		37·0	26·3	56·6	26·0	36·8	50·0	49·6	69·0	27·3	47·3	32·0	27·7	35·4	34·3	41·4	38·9	40·4	27·3	52·8	46·9	39·0	47·6
Percentage of total fat split		89·0	77·4	86·4	52·0	86·4	92·5	86·9	90·5	86·2	87·3	85·0	84·0	75·1	84·0	85·4	80·6	76·6	70·2	80·1	60·3	88·4	83·9
Percentage of total fat unsplit		11·0	22·6	13·6	48·0	13·6	7·5	13·1	9·5	13·8	12·7	15·0	16·0	24·9	16·0	14·6	19·4	23·4	29·8	19·9	39·7	11·6	16·1
Duodenal Juice	Trypsin ml. of 1% casein sol.	present			present				50		20	25	200	50	20	20		100	10		50	present	20
	Lipase ml. of N/10 sodium hydroxide	0·1							0·2		0·2	1·9	0·1	0·2		0·2			0·1		2·0		0·3

of duodenal juice was found to be between 20 and 200 ml. in ten of the cases and to be 10 ml. in the other case. Lipase was estimated in nine cases, and the number of ml. of N/10 sodium hydroxide will be seen to range from 0·1 to 2·0 ml. (normal, 0·2 to 2·0) and to be at, or above, the lower limit of normal in six.

Fractional test meals. Normal acid curves were found in twelve patients (54·6 per cent.), low acid curves in nine (41 per cent.) and absent free and combined acid in one (4·4 per cent.).

Blood sugar estimations. The minimum fasting level obtained was 55 mg. per 100 ml. and the maximum 174 mg. per 100 ml. It lay between 55 mg. and 99 mg. per 100 ml. in seven patients and between 100 mg. and 174 mg. per 100 ml. in fifteen. In the oral glucose tolerance test blood sugar estimations were only possible at half-hourly intervals up to two hours after the ingestion of glucose, and some of the patients were inadvertently given glucose in excess of 1 g. per kg. of body weight. The results obtained in this series are, therefore, of limited significance.

An initial fall of the type described by Emery (1947) was observed in two patients: in one the blood sugar failed to return to the fasting level by two hours after the ingestion of glucose: in the other, it returned to, but not above, the fasting level. In only eight patients was there a rise of less than 40 mg. per 100 ml. above the fasting level: in seven, of 40 to 69 mg. inclusive: in two, of 70 to 99 mg. and in three of 100 to 150 mg.

Blood plasma protein, etc. The findings for blood plasma protein, serum calcium, inorganic phosphate, and alkaline phosphatase are summarized in table 2. Plasma protein will be seen to have ranged from 5·8 to 9·5 mg. per 100 ml. (normal = 6·0 to 7·3). These high values were accounted for by the copper sulphate solution used in Van Slyke's method being found to be below standard.

The values for serum calcium ranged from 7·1 to 11 mg. per 100 ml. (normal = 9·0 to 11·0); for inorganic phosphate from 1·6 to 3·75 mg. per 100 ml. (normal = 4·0 to 6·0), and for alkaline phosphatase from 5 to 31 units (normal = 3 to 31 units).

The blood haemoglobin will be seen from table 3 to have ranged from 40 per cent. to 85 per cent., being between 50 per cent. and 59 per cent. in four cases, between 60 per cent. and 74 per cent. in seven cases, and over 65 per cent. in eleven cases. The red blood cells numbered from 3·3 to 6·8 million per c.mm. The colour index was less than 1·0 in all cases. The sternal bone marrow showed no

TABLE 2
THE FINDINGS FOR BLOOD PLASMA, PROTEIN, SERUM CALCIUM, INORGANIC PHOSPHATE, AND ALKALINE PHOSPHATASE

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Plasma protein g. per 100 ml	8·9	6·15	8·2	8·9	7·85			8·1	7·1	6·4	9·5	6·15	7·5		8·6	6·8	8·2	7·15		5·8	9·5	
Serum calcium mg. per 100 ml.	10·3	10·5	10·0	9·0	7·1	10·6		10·0	10·8	9·0	11·0		11·0		9·2	8·5	10·8	9·0	10·2	9·0	10·0	7·25
Inorganic phosphate (mg. per 100 ml.)	1·6			3·0	3·75			2·4			3·0		2·3							2·3	2·8	2·0
Alkaline phosphatase (units per 100 ml.)		10	16	8	15	5	7·5	20	14	10	25		31	6	11	18	10	10	15	15	5	5

megaloblastic erythropoiesis in any of the six cases examined.

Radiological appearances. In all cases segmentation of the barium in the small intestine with loss of the normal haustration compatible with a diagnosis of coeliac disease was seen in radiographs of the small intestine following a barium meal. In three cases (13·9 per cent.) these changes were only slight.

Radiographs showed rickets to be present in two cases (9·9 per cent.), osteoporosis in sixteen (72·7 per cent.): no relationship was demonstrable between the presence of osteoporosis and the level of alkaline phosphatase. Delayed ossification in the epiphyses of the wrists was found in nine patients (40·9 per cent.).

Radiological evidence of pulmonary fibrosis was present in one case only (4·5 per cent.).

Results of Treatment

Twelve cases (A1) showed slight increase in weight on preliminary treatment; of these, eight (A2) showed further slight increase in weight accompanying folic acid administration.

Ten cases (B1) showed no increase in weight on preliminary treatment: and of these, eight (B2) showed slight increase in weight on folic acid.

Twelve cases (C1) (eight of which were included in group A1) showed improvement in faeces on preliminary treatment. Of these nine (C2) maintained this improvement or showed further improvement accompanying folic acid administration.

Ten cases (D1) showed no improvement in faeces on preliminary treatment: and of these seven (D2) showed improvement on folic acid.

Of the twenty-two cases, therefore, sixteen (twelve of group A1 plus four of Group C1 not included in group A1) may be said to have shown slight clinical improvement on preliminary treatment, and twenty-one (eight of group A2, plus five of group C2 not included in group A2, plus five of group B2 not included in groups A2 or C2, plus three of group D2 not included in groups A2, B2 or C2) further clinical improvement, or improvement in those cases where there had been none on preliminary treatment, accompanying folic acid administration: that is, improvement which might be attributed to folic acid.

The actual measurement of this improvement, however, by rate of gain in weight showed it to be very slight indeed. The average gain for all the cases per month on preliminary treatment alone was only 0·4 lb., and on preliminary treatment plus folic acid 0·5 lb.: and in the cases which improved on preliminary treatment alone the average gain was 0·9 lb., and in those which improved or further improved on folic acid 1·2 lb.

Such small differences in the rates of gain during the periods under comparison do not provide convincing evidence of any beneficial effect of folic acid; especially in view of the fact that the majority of the children were much underweight at the beginning of treatment.

Observation of the haemoglobin during treatment in the six cases where it was possible also revealed no uniform beneficial effect. In five of the cases no rise of haemoglobin occurred during the period of preliminary treatment or of folic acid administration, and in the sixth some increase of haemoglobin was observed during both periods.

Conclusions

This clinical trial of folic acid in twenty-two cases of coeliac disease, in none of which there was a macrocytic anaemia, would appear, therefore, to support May's findings in his five similar cases: namely, that there is no definite evidence of any effect on the progress of the condition.

In the absence of macrocytic anaemia in any of these cases a comparison with Thompson's results with folic acid administration in this type of anaemia complicating coeliac disease is not possible.

Summary

Twenty-two infants and children considered to be suffering from coeliac disease were treated for a period with a low-fat and high-protein diet, liver extract, and vitamins. Folic acid was then added to the treatment for a comparable period. The clinical condition of the children during these periods was compared by observations on rate of gain in weight and on the naked-eye character of the faeces.

No conclusive evidence was obtained of any beneficial effect of the folic acid.

TABLE 3

BLOOD HAEMOGLOBIN, RED CELLS, COLOUR INDEX, AND STERNAL MARROW FINDINGS

Cases	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Haemoglobin (%)	67	85	50	70	50	75	75	75	80	85	56	65	75	80	85	55	85	70	90	60	65	60
Red blood cells (millions per c.mm.)	5·6		3·7	5·0	3·3			3·9		4·5	3·8	4·0	4·9			3·5				3·5	6·8	4·2
Colour index	·58		·67	·7	·8			·96		·9	·72	·8	·77			·78				·85	·48	·71
Sternal marrow normoblastic erythropoiesis		+	+						+								+		+	+		

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THE NITROGEN PARTITION IN NEWBORN INFANTS' URINE

BY

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There appears to be very little information on the partition of nitrogen in the urine of infants during the first week of life comparable to the figures produced by Folin (1905a), and by subsequent workers for adult urine. Simon (1911), however, showed that the amino and undetermined nitrogen formed a greater proportion of the total urinary nitrogen in newborn infants than in adults. Schloss and Crawford (1911) measured the total nitrogen, uric acid, and purine excretion in newborn infants, and found that the output of uric acid rose considerably during the first three days of life, and subsequently fell.

Most of the work on nitrogen metabolism in infancy has been done on infants aged two weeks or more, by which time life has become more stable. Colostrum has given place to milk, and the intake of the latter is no longer rising very fast. The physiological dehydration of the first few days has passed, and meconium is no longer being excreted. Studies in nitrogen metabolism made during the first few days of life have, however, a particular value, for they help to bridge the gap between foetal and postnatal metabolism. Unfortunately, the quantities of metabolites excreted during the first few days of life are not necessarily the same as those actually produced by the organism, for Balint and Stransky (1920) and McCance and Widdowson (1947) have shown that the dehydration during the first three or four days of life is accompanied by a rise in the urea and non-protein-nitrogen in the body fluids. Consequently, the end products of nitrogen metabolism will not be excreted so rapidly as they are produced during the first three or four days, and rather more rapidly during the ensuing days.

The present work was undertaken to provide further information on the partition of nitrogen in the urine of very young infants, and on their daily output of certain nitrogenous substances.

Materials and Methods

Specimens were obtained from the maternity wards of two hospitals in Wuppertal, the Seventy-Seventh British General Military Hospital, and the Landesfrauenklinik.

No consistent difference was found between the British infants at the military hospital and the German infants at the civilian hospital, although the nutritional status of the German mothers at the latter may not have been altogether satisfactory, since the work was done between the Autumn of 1947 and the Spring of 1948, when the German population were still on rather a poor diet. Any effect that the nutritional status of the parent may have had upon her offspring was masked by individual variations, and the number of subjects was not large enough for such an effect to receive statistical treatment.

For technical reasons, only male babies were studied. Single untimed specimens were obtained by fixing a test tube over the penis. Continuous collections were made with an apparatus designed by R. F. A. Dean. This consisted of a glass tube 24 mm. in diameter, ample enough to accommodate the penis, moulded and slightly flanged at the upper end to fit closely to the skin without actually touching the penis at all. A hole in the upper surface allowed equilibration of pressure, and prevented the formation of air locks. The lower end was narrowed for the attachment of a rubber tube, which led down to a bottle containing toluene. The whole apparatus was suspended from a belt round the infant's abdomen. Continuous collections have been made for as many as nine days with this apparatus, without any difficulties being encountered.

The urines were collected from normal full-term infants, which were subject to the regular hospital routine. Breast feeding was started twenty-four to thirty-six hours after birth, and no child received any fluid earlier than this. On a single occasion 30 ml. of 'tea' was given to each of two babies to supplement their fluid intake during the first day of breast feeding. The urines were preserved with toluene. Protein was found in small quantities in a few specimens, and, when present, was removed by filtration after boiling with a few drops of glacial acetic acid.

The total nitrogen was estimated by the micro-kjeldahl method, using copper selenide and copper sulphate as catalysts. Ammonia was estimated on the day of collection, before removal of protein

TABLE 1

A COMPARISON OF THE CONCENTRATIONS OF TOTAL NITROGEN AND OF THE NITROGEN PARTITION IN INFANT AND ADULT URINES

Age and diet	No. of subjects	Average total nitrogen mg./100 ml. urine	These figures are expressed as percentage of the total nitrogen					
			Urea N	Ammonia N	Creatinine N	Creatine N	Uric acid N	Undetermined N
At birth	11	97	71·1	5·4	3·4	2·0	4·9	13·2
0–12 hours	12	468	56·9	7·2	4·1	1·9	5·8	24·1
12–24 hours	10	704	60·4	8·5	5·4	2·1	5·6	18·0
48–72 hours: breast milk	12	812	65·5	7·0	3·9	2·1	4·0	17·5
Adults: normal (present investigation)	10	919	82·7	4·6	3·7	1·0	1·6	6·4
Adults: normal (Folin, 1905a)	6	—	87·5	4·3	3·6	—	0·8	3·8
Adult: Normal (Cathcart, 1907)	1	—	87·1	3·6	3·2	0·1	1·0	5·0
Adult: 14th day of starvation (Cathcart, 1907) ..	1	—	77	9·4	3·1	1·3	2·2	7·0
Adult: 21st day of starvation (Benedict, see Lusk, 1928) ..	1	—	69·9	19·8	4·8		1·4	4·1
Adults: high-calorie–low-protein (Folin, 1905b)	3	—	60·6	9·7	15	—	3·2	11·5
Adults: high-calorie–low-protein (Robison, 1922)	2	—	48	11·1	21·7	—	3·4	15·8

(if present), by the microdiffusion method of Conway and Byrne (1933, 1935). Urea was estimated by the method of Archibald (1945) and, since a high degree of accuracy was required in view of the large proportion of urea in the total nitrogen, some determinations were also made by the urease method of van Slyke and Cullen (1914) with very good agreement. Creatinine and creatine were estimated by the method of Folin and Wu (1914). Uric acid was estimated by the method of Benedict and Franke (1922), but since the results obtained by this method were somewhat lower than those previously reported for uric acid in infants' urines (Schloss and Crawford, 1911), a number of estimations were also performed by the silver nitrate precipitation method of Folin (1933). The values given by the latter method averaged slightly less than those given by Benedict and Franke's direct method, but in no case would the difference between the two methods involve an alteration in the undetermined nitrogen greater than 1 per cent. Further confirmation that the uric acid values were correct was provided by the determinations of purine nitrogen which, in most cases, only slightly exceeded the uric acid nitrogen. If the urines had contained as much uric acid as those reported in the literature, they would have held more uric acid nitrogen than the total purine nitrogen, which would have been absurd. The total purine nitrogen was estimated by the method of Hitchings and Fiske (1941). The free amino nitrogen was estimated by Frame et al's (1943) modification of the method of Folin (1922), and combined amino nitrogen by the same method after hydrolysis with 20 per cent. hydrochloric acid or 20 per cent. sodium hydroxide for one hour. Acid and alkaline hydrolysis released practically the same amount of amino nitrogen from aliquots of the same urine.

Results

Table 1 shows the total nitrogen in mg. per 100 ml. of urine, and the nitrogen partition in specimens of urine passed at birth, in the next twelve hours of life, between the twelfth and twenty-fourth hour, and between the forty-eighth and seventy-second hour. Data obtained by the same methods on the urines of five men and five women on normal diets are also given. Figures obtained from the literature for adults on normal diets (Folin, 1905a), under conditions of starvation (Cathcart, 1907; Benedict, quoted by Lusk, 1928), and on high-calorie–low-protein diets (Folin, 1905b; Robison, 1922). It will be seen that the present findings for normal adult urines are in fairly good agreement with those of Folin (1905a) and of Cathcart (1907).

The eleven urines passed at birth were produced within a few minutes of the baby leaving the uterus, and were formed there. It can be seen from table 1 that the quantity of nitrogen per 100 ml. was extremely small. During the first few days the concentration of total nitrogen increased, and the highest average was reached between the forty-eighth and the seventy-second hour, when physiological dehydration is usually greatest, but even at this time the urine contained less nitrogen per 100 ml. than the average daily urine of an adult.

TABLE 2
THE PURINE AND AMINO NITROGEN IN INFANT AND ADULT URINES

	No. of specimens	Total nitrogen mg./100 ml. urine	Purines other than uric acid (% of T.N.)	No. of specimens	Total nitrogen mg./100 ml. urine	Amino nitrogen % of T.N.	No. of specimens	Total nitrogen mg./100 ml. urine	Amino nitrogen released by hydrolysis (% of T.N.)
Infants, 0–24 hrs. . .	5	559	1·57	10	476	3·3	5	543	0·9
Infants, 24–48 hrs.	5	661	1·4	10	646	2·6	—	—	—
Adults, normal diet	6	870	0·35	5	842	0·9	5	925	0·5

The partition of nitrogen in infants' urines differed considerably from that in the urine of adults on a normal diet, for (1) the urea formed a much smaller percentage of the total nitrogen, so much so that the ranges of individual variation did not overlap. The data for normal adult urines taken from the literature show that the figure now given for adults was not unusually high; it was, in fact, lower than that of Folin or of Cathcart. (2) The ammonia formed a significantly greater percentage of the total nitrogen, a finding which agrees with that of McCance and von Finck (1947), who found in their series also that the difference was statistically significant. (3) The creatinine accounted for very nearly the same percentage of the total nitrogen. Since these infants (see later) excreted less total nitrogen per kg. of body weight per day than adults did, this means that they also excreted less creatinine per kg. of body weight, an observation which agrees with the one made by Rose in 1911. (4) The creatine nitrogen made up a higher percentage of the total nitrogen. This was to be expected, since men have been said to excrete no creatine. Actually, in this work, both men and women were found to excrete similar but very small amounts. (5) The uric-acid nitrogen accounted for about three times as much of the total nitrogen, and (6) the undetermined nitrogen made up a much greater percentage of the total nitrogen. It varied inversely, as might have been expected, with the percentage excreted as urea, and reached the remarkably high average figure of 24 per cent. in the first twelve hours of life.

Table 2 contains a partial analysis of the 'undetermined' nitrogen of infant and adult urines. It will be seen that the nitrogen of purines other than uric acid, and of free and conjugated amino acids, made up a greater proportion of the total nitrogen in the infants' than in the adults' urines, but these findings did not account for very much of the undetermined nitrogen.

When the figures for infants in table 1 are compared with those drawn from the literature for

TABLE 3
VARIATIONS IN THE DAILY OUTPUT OF TOTAL NITROGEN, UREA, AND URIC ACID DURING THE FIRST WEEK OF LIFE, AND A COMPARISON WITH ADULTS

	8 infants: age in hr.			Adults and diet						
				Normal diet			Starvation		High-calorie–low-protein	
	0–48	48–96	96–144	4 adults present investigation	Folin (1905a) 6	Cathcart (1907) 1	Cathcart (1907) 1	Benedict (1915) 1	Folin (1905b) 3	Robison (1922) 2
Total nitrogen mg/day	119·8	147·6	190·7	11,715	16,000	15,970	7,780	7,930	3,300	2,070
Urea nitrogen mg./day	68·4	89·2	123·6	9,627	13,900	13,920	5,990	5,540	2,000	995
Uric acid nitrogen mg./day	6	6	6·8	166	120	157	170	112	103	70
Urea nitrogen as % of total nitrogen . .	59·4	64·3	67·9	82	87·5	87·1	77	69·9	60·6	48
Uric acid nitrogen as % of total nitrogen	7·3	4·4	3·7	1·4	0·8	1·0	2·2	1·4	3·2	3·4
Total nitrogen mg./kg./24 hrs.	30·5	38·6	49·9	203	255	242	135	158	47·3	34·4
Urea nitrogen mg./kg./24 hrs.	18·3	25·1	33·9	167	223	212	104	112	28·6	16·5
Uric acid nitrogen mg./kg./24 hrs. . .	1·6	1·7	1·8	2·9	2·0	2·4	2·9	2·2	1·5	1·6

adults on abnormal dietary regimes, certain interesting points emerge. (1) The percentage of the total nitrogen excreted as urea by adults has been found to be lower in starvation than on normal diets, and to be lower still on high-calorie–low-protein diets. The figures for infants lay between the starvation and low protein levels for adults. (2) The percentage of the total nitrogen excreted as ammonia by starving adults, and by adults on high-calorie–low-protein diets has been found to be higher than normal, and the figures obtained were somewhat higher than those now being reported for infants. (3) The percentage of the total nitrogen excreted as creatinine by infants is similar to that excreted by starving adults, but very much lower than that excreted by adults on high-calorie–low-protein diets. (4) The percentage of the total nitrogen excreted as uric acid by infants was not only higher than that excreted by normal adults, but somewhat higher than that excreted by starving adults or adults on a high-calorie–low-protein diet.

Further reference to table 1 shows that the percentage of the total nitrogen excreted as urea by the infants varied with age. Thus at birth it was 71·1 per cent., in the next twelve hours it fell to 56·9 per cent., and on the third day rose to 65·5 per cent., and these differences were statistically significant ($t = 2{\cdot}69$, $p = 0{\cdot}02$; and $t = 2{\cdot}45$, $p = 0{\cdot}03$ respectively). As may be seen from table 3, the rise continued at least until the sixth day.

Table 3 shows the average total nitrogen, urea, and uric acid nitrogen excreted in twenty-four hours by eight infants during the first six days of their lives in three periods of two days each. The average amounts of these substances excreted in single twenty-four hour specimens by three men and one woman on normal diets, and figures obtained from the literature for the excretion of the same metabolites by adults on abnormal dietary regimes are also given. The upper part of the table shows the excretion in mg. per twenty-four hours, the middle part the percentages of the total nitrogen formed by urea and uric acid, and the lower part the excretion of these substances in mg. per kg. of body weight per twenty-four hours. The results were not obtained from the same specimens of urine as those given in table 1, but they show the same features. The urea formed a considerably lower percentage of the total nitrogen than it did in adults on normal diets, and there was again a rise between the first two and the last two days of the period of observation. The percentage of the total nitrogen made up by uric acid was considerably greater than in normal adults, but it tended to fall and was only slightly higher at the close of the period of observation than in adults on high-calorie–low-protein diets.

There was sometimes considerable variation in the amount of total nitrogen excreted by the same infant from day to day, but it is not thought possible that this was due to spilling of part of the urine, for when this did happen in other infants it was made obvious by the dampness of the napkin surrounding the collecting apparatus. It is thought that these day-to-day variations were due to irregularities in the times at which the infant voided its urine and to retention in the bladder of variable amounts, so that urine secreted during one twenty-four hour period was collected with the next.

Table 3 also makes it clear that (1) the daily excretion of total and of urea nitrogen tended to rise, but it was always much lower per kg. of body weight per twenty-four hours in the infants than in the normal or the starving adults, and was about equal to the figures which have been found for adults on a high-calorie–low-protein diet. (2) The infants excreted less uric acid per kg. of body weight per twenty-four hours than normal or starving adults, but about the same amount as adults on a high-calorie–low-protein diet. The amount excreted per day was nearly constant, a finding which directly conflicts with that of Schloss and Crawford (1911). The difference may lie in the technique by which the urine was collected and sampled (see above), or by which the uric acid was estimated, or even in the dietary treatment of the children (Reusing, 1895; Birk, 1911). As already stated, the figures obtained for infants in the present investigation were lower than those obtained by Reusing or Simon, or by Schloss and Crawford, but no studies of the uric acid metabolism in the first week of life have appeared since the more modern chemical techniques were introduced. The figures obtained for adults in this study, however, were in complete agreement with those of others (table 3).

Discussion

A comparison of the amounts and types of nitrogenous compounds excreted by infants and adults has brought out certain differences and similarities. These are clearly not all due to one and the same cause, but a number of them can be explained in terms of what is already known about metabolism. In adults on a normal diet the excretion of nitrogen is high because the protein intake is generous and little or none of the nitrogen is being retained or excreted by extra-renal channels (*Lancet*, 1937). The excretion of nitrogen may also be very high, due to the destruction of body protein which follows trauma or burns. It falls during starvation because the breakdown of protein is not so rapid at that time as it is after trauma, or during periods of luxus consumption and higher metabolic rates. It falls greatly on high-calorie–low-protein diets, because the high intakes of sugar and fat reduce the breakdown of body protein for gluconeogenesis.

The percentage of the total nitrogen in the urine present as urea is high in normal adults, or in adults after trauma, because the catabolism of protein is sufficiently rapid to ensure that the urinary nitrogen is greatly in excess of the amount required for the prior charges, such as ammonia and creatinine. This statement is true regardless of the theories which may at any time be held about the sources

of these compounds. The percentage falls in starvation because the amount of nitrogen required for the prior charges falls less than the quantity of nitrogen set free from the protein catabolized, and this tendency is accentuated by a high-calorie–low-protein diet. In other words, in the absence of disturbing factors such as acidosis, the greater the amount of nitrogen to be excreted, the greater will be the percentage of that nitrogen excreted as urea and the smaller will be the percentage excreted as ammonia or creatinine.

Total nitrogen. For the first forty-eight hours of a breast-fed infant's life its output of nitrogen would be expected to be low (a) because it is starving, (b) because its total expenditure of energy at that time is small, and therefore the breakdown of tissue protein is likely to be correspondingly small, and (c) because the kidney does not excrete all the nitrogen which is broken down. Furthermore, the ratio of nitrogen excreted to nitrogen ingested is likely to be lower in infants than in adults, because the dietary nitrogen will always tend to be used to increase the mass of body protein. This is not important during the first forty-eight hours of life, because the ingestion of food is so small at that time; but, on intakes of nitrogen and calories which are adequate in terms of body weight, infants would be expected to excrete less nitrogen than adults, and to excrete a smaller percentage of that nitrogen as urea.

One can, therefore, explain along these lines why the output of nitrogen per kg. of body weight in infants should bear the relationship it has been found to do to normal and starving adults, and to adults who have been placed on high-calorie–low-protein diets. It would appear from table 3, however, that in the critical days after birth the amount of nitrogen excreted per twenty-four hours increases with age. This rise can be explained in a similar way, for in the first two days of life the baby is starving, and becoming dehydrated, whereas at the end of the first week it is taking a sufficient quantity of food and fluid to meet practically all its excretory and metabolic requirements.

Urea nitrogen. For the reasons already given, the percentage of the total nitrogen excreted by infants as urea would be expected to be lower at all times than that excreted by normal adults, but it also varies in an interesting way with age within the first week (tables 1 and 3). 71·1 per cent. of the nitrogen in the urine formed in utero was present as urea, and it is suggested that this is an expression of the fact that the urine came from a well-fed but actively growing organism. It was mainly the active growth which kept the percentage of the total nitrogen excreted as urea below that of normal adults. With the onset of starvation the percentage excreted as urea fell, for the reasons already given for its fall in starving adults. There was no significant difference between the percentage excreted as urea in the first and second twelve hours of life, but the lower figure obtained for the first twelve hours may possibly have been due to the fact that the baby was born with a sufficient store of glycogen in its liver to delay gluconeogenesis for that period of time. A significant rise in the percentage of the total nitrogen excreted as urea was, however, apparent by the third day, by which time the infants were beginning to take a relatively high protein diet and the output of nitrogen was increasing. It would appear from table 3 that the rise in the output of nitrogen, and therefore in the percentage of that nitrogen excreted as urea, continues for some time after birth.

Ammonia nitrogen. The percentage of the total nitrogen found to be excreted as ammonia by normal adults in the present investigation is close to that found by Folin (1905a) and Cathcart (1907), but below the percentage excreted as ammonia in adults who are starving or taking high-calorie–low-protein diets. The rise in starvation has generally been accepted as due to the acidosis (Lusk, 1928) and the increase on high-calorie–low-protein diets to the small amount of total nitrogen in the urine. However, examination of the figures of Folin and of Cathcart for adults on normal and on high-calorie–low-protein diets reveals that the actual quantity of ammonia excreted per kg. of body weight in twenty-four hours is lower on the latter (averaging 10 mg. per kg. per twenty-four hours on normal, and 5 to 6 mg. per kg. per twenty-four hours on high-calorie–low-protein diets). The high figures in infancy were attributed by McCance and von Finck to the fact that the urine at this age contained so little inorganic phosphate. From the point of view of ammonia production this is equivalent to an acidosis, because, if the urine is to be maintained above pH5 in the absence of the usual buffering substances, much more of the acids have to be excreted as their ammonium salts. There may also be a real acidosis at that age, but even if there is the quantity of ammonia excreted per kg. per twenty-four hours remains less in infants than in normal adults, for table 1 shows that the percentage of the total nitrogen formed by ammonia in infants' urine is not more than double that in normal adults' urine, and table 3 shows that the total nitrogen excreted per kg. body weight in twenty-four hours by normal adults is at least four times that excreted by infants, even at the end of the first week of life.

Uric acid nitrogen. In infancy the large percentage of the total nitrogen excreted as uric acid at once arrests attention. This is not due to a large production of uric acid per kg. of body weight as the appearance of an infant's urine on the second day of life might suggest, or as the deposits of uric acid in the kidney of the newborn have led many to suppose. Actually, the excretion of uric acid per kg. of body weight is lower in infants than in adults, except when the latter are on high-calorie–low-protein diets. This may be partly an expression of the fact that an infant's food is practically purine-free. At all events physicochemical conditions in the urine rather than the large amounts of urates there must underlie the ready deposition of urates from

infant urines. The high percentage of the total nitrogen excreted as uric acid in infancy must be attributed primarily to the fact that the total nitrogen excreted per kg. of body weight is so low, and the reasons for this have already been discussed. It is certainly not due, as it may be in adults, to a high-calorie–low-protein diet. There is no doubt, however, that the ratio of uric acid nitrogen to urea or to total nitrogen in the urine is very much higher in early infancy than in later life, and this suggests that infants may convert more of the available amino acids to purines than adults do, in other words that their purine metabolism is relatively more intense.

Undetermined nitrogen. The percentage of the total nitrogen unaccounted for in the urine of infants is remarkably high, and is only approached by adults who are on high-calorie–low-protein diets. It has been shown that this large fraction cannot be accounted for as purines other than uric acid, or as amino nitrogen, either free or combined. It may, as with uric acid, be due partly to the very small output of total nitrogen, but the nature of this undetermined nitrogen awaits investigation. There are indications, however, that the quantities and amounts of the different amino acids which are excreted at this age may differ considerably from those found in later life, and this matter is being studied at the present time.

Summary

1. The total nitrogen in urine formed in utero averaged less than 100 mg. per 100 ml. When physiological dehydration was greatest the total nitrogen averaged 812 mg. per 100 ml., but this was not so high as the average figure found in normal adult urine.

2. During the first week of life the outputs of total and urea nitrogen, expressed as mg. per kg. of body weight per day, tended to rise but were always much lower than they were in normal or starving adults. They were about equal to the outputs of adults on high-calorie–low-protein diets. The output of uric acid nitrogen in mg. per kg. per day was also much lower than in normal or starving adults, but there was no tendency for it to rise.

3. When the partition of nitrogen in infants' urine was compared with that in normal adults' urine it was found that (a) the percentage present as urea was lower, (b) the percentage present as ammonia, uric acid, and undetermined nitrogen was higher, (c) the percentage present as creatinine was about the same.

4. The percentage of the total nitrogen present as urea was significantly higher in the urine formed in utero and after the third day of life than in that passed in the first two days of life.

5. By comparing these results with those for starving adults and for adults on high-calorie–low-protein diets, and by taking into account what is known of the nitrogen metabolism of adults and infants, most of these findings can be explained.

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PERINATAL DEATHS IN CZECHOSLOVAKIA*

BY

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Macgregor (1946) is certainly right in saying that the pathology of stillbirth and of the neonatal period is still a somewhat neglected field. So it was in my department until 1940. In fact, the bodies of stillborn foetuses were for the most part delivered directly to the department of normal anatomy and thus completely escaped adequate post-mortem study. This, however, was stopped after the closing of the Czech university by the Germans in 1940, and since that time I have had complete post-mortem material of this kind, owing to the fact that in Czechoslovakia necropsies are compulsory in people who have died in public hospitals.

My interest in this subject was also aroused by the magnificent work of Potter et al. (1940) in Chicago. But it seems that there has been a general trend towards the study of this question, as several papers on this subject have since appeared. In Great Britain remarkable work has been done by Macgregor (1946) in Edinburgh, Evans and Smith (1946) in Manchester, Baird (1945), Russ and Strong (1946), and others. In Russia, the work of Morozova (1946) and Komarova (1946) is on similar lines.

There are two main reasons for presenting my own material. First, it is more extensive than other published material except Potter's. This means that statistical errors due to small numbers are reduced. Secondly, it may be of interest to compare the ' perinatal ' mortality in my country with that in the United Kingdom as far as this can be done in view of the somewhat differing criteria.

' Perinatal Mortality ' Period

The term ' perinatal mortality ' has been used for a long time by French obstetricians. It seems practical, as it comprises deaths before, during, and after delivery. Its delimitation, however, is arbitrary in two respects. First, there exists some uncertainty as to the lower limit of prematurity. Very premature, obviously non-viable foetuses are sometimes discarded as abortions, and no accurate limit for this is indicated. This of course may influence the figures. I have kept to the criteria suggested by Potter, who has set the limit as low as 400 g. in weight. This means that all foetuses above this weight are included in my statistics.

Secondly, the upper limit of the period considered as neonatal is subjected to similar variation. With Potter it was originally a fortnight, but later she extended it to one month. The latter period is usually accepted by British authors.

In my statistics, however, it was only ten days. The reason for this lies partly in the fact that I was originally concerned especially with causes of deaths consequent on birth stress, and partly to practical circumstances. As mothers, owing to shortage of beds, are usually dismissed from the maternity unit in Prague within ten days, it would have been very difficult to follow up the children longer than that. Babies who appear ill are, to be sure, immediately transferred to the children's clinics, from which the necropsies are also performed by me. Nevertheless, some of the deaths occurring after the tenth day of life might escape, and this would lessen the reliability of my statistics. Owing to this difference my figures are not exactly comparable with those of the British authors previously named. On the other hand, the difference cannot be of much importance, considering the fact that by far the greater number of neonatal deaths occur within the first few days after birth. This is clearly shown by fig. 1, which shows the distribution of deaths in the first ten days. From this it will be seen that if the

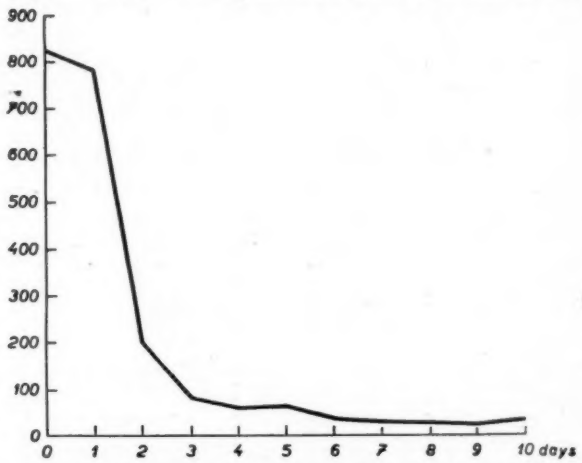

FIG. 1.—Number of deaths within the first ten days.

* Paper read at The Hospital for Sick Children, Great Ormond Street, London, July 9, 1947.

upper limit of the neonatal period is extended to one month some additional deaths will be included, but the difference will not be very large.

The Material Presented

The necropsies to which my statistics refer all came from the maternity unit in Prague. There are three obstetrical departments there, one of which, however, was German until the end of the war, during which period its necropsies were not performed by me. There is also a private-patient department, and this is included in my material. In the period 1943-6, that is in four years, there were 38,999 births in these clinics. There were 862 stillbirths, that is 22·1 per 1,000, and 1,334 neonatal deaths (34·1 per 1,000); the total number of deaths was 2,196, which means a mortality of 56·2 per 1,000. In forty-nine necropsy could not be performed for various reasons, so that my statistics are based on 2,147 necropsies.

I do not contend that these figures are representative of the country as a whole. In the clinics the standard of obstetrical care is always higher than in general practice; on the other hand, however, complicated cases are likely to be sent to the clinics, and this tends to raise the mortality. As far as I was able to get information from the State Statistical Department, the stillbirth rate was from 15·0 to 15·5 per 1,000 in Bohemia and Moravia, but it seems that the borderline between abortions and prematurity has been set somewhat higher than in my material. The neonatal death rate up to the fifteenth day of life was 34·3 per 1,000 in 1943 and 32·2 in 1944, which is about the same as in the clinic.

These figures indicate that approximately every twentieth pregnancy ends with death of the child in the perinatal period. This obviously means a tremendous loss of national energy, and it is therefore not surprising that so much work has recently been devoted all over the world to the analysis of the causes of the perinatal mortality.

On the other hand, I believe that the conditions in my country, concerning perinatal deaths, do not compare unfavourably with those in other countries. Baird says that in England the average stillbirth rate in 1938 was 38·27 per 1,000, whereas for Greater London in 1939-41 it was 30·0. In Scotland, according to the Registrar General's figures, the stillbirth rate for 1943–1945 was 33·6; the neonatal mortality rate over the same period was 30·4.

Sex ratio. Of the 39,000 births 20,303 were boys, and 18,696 were girls (table 1). Thus there was a surplus of 1,607 boys, and the sex ratio was 108·5 : 100. It is a well established fact that slightly more boys are born in general, and this disproportion is said to be consistently increased during wars. Although Czechoslovakia was not exactly at war, it nevertheless seems that the same conditions were prevalent. On the other hand, the rates both of stillbirths and neonatal deaths are considerably higher in boys than in girls. In my material the total perinatal mortality for boys was 59·6, and that for girls 52·6. Thus boys are markedly more susceptible to the causes of perinatal death, though the difference, 226 cases, was not large enough to compensate for their higher birth rate.

Causes of death. In table 2 a synopsis is given of the causes of death, as they were established at necropsy. Single causes of death show much overlapping. A newborn may for instance have intracranial haemorrhage and pneumonia at the same time, and it is a matter of conjecture which condition is considered the main cause of death. This overlapping is particularly prevalent between asphyxia and intracranial haemorrhage, so that I felt it necessary to include such cases under a separate heading.

Otherwise the table is self-explanatory, and there is no need to go into a detailed discussion of the single causes of death as this has been recently done by Macgregor and others in this country. Nevertheless some comment seems indispensable.

The cases are divided into two groups, prenatal deaths and neonatal deaths. The criteria for life at birth were the usual ones, but it was sometimes difficult to decide whether the child had been born dead or living, and there were also some discrepancies between the clinical and pathological findings.

Each group is divided according to maturity at birth. As to the criteria of non-viability, viability, maturity, and postmaturity, these are always arbitrary. I have kept to those given by Potter, chiefly as far as weight is concerned. That is, foetuses weighing from 400 to 1,000 g. are classified as non-viable, those between 1,000 and 2,500 as immature* but viable, and those over 4,500 g. as postmature. This, of course, is a very rough estimate, as there is no doubt that foetuses born at term may be less than 2,500 g., particularly if they are twins or triplets, and, on the other hand, sometimes a foetus born before term may be more than 2,500 g. But as, with a few exceptions, the differentiation of the organs keeps pace with weight, this rough estimate may well serve the purpose in question. As to viability, foetuses under 1,300 g. seldom survive, and the deaths in this class make up most of cases in which no other cause of death than immaturity can be demonstrated, and which I have classified under the heading of debility.

ASPHYXIA. As in any statistics of perinatal death, the most frequent cause of death appears to be asphyxia. If the cases of protracted asphyxia due to inhalation of foreign material as well as those where asphyxia is combined with haemorrhage are included, it makes a total of 31·7 per cent. This is considerably less than the figure arrived at by Macgregor, but one must keep in mind that in the hospital series she studied (Macgregor, 1943),

* I am using the term 'immature' instead of 'premature,' because, logically, delivery may be premature but the child is immature.

TABLE 1
SEX RATIOS OF BIRTHS AND PERINATAL DEATHS

Sex	Number of births	Sex ratio	Perinatal deaths	Death rate per 1,000	Sex ratio
Boys ..	20·303	108·5 : 100·0	1,211	59·6	122·9 : 100·0
Girls ..	18·696		985	52·6	
Difference ..	1·607		226	7·0	

TABLE 3
MATURITY AND PREMATURITY

	Number of births	Stillborn	Neonatal deaths	Total deaths	Death rate per 1,000
Mature ..	34,097	351	318	669	19·7
Premature	4,902	480	998	1,478	301·7
	38,999	831	1,316	2,147	

TABLE 2
CAUSES OF DEATH AS ESTABLISHED AT NECROPSY

Cause of death	Prenatal					Neonatal					Total prenatal plus neonatal	%	Ratio of boys to girls	Immature	Mature	Correspondence of clinical diagnosis	%
	Immature		Mature	Post-mature	Total	Immature		Mature	Post-mature	Total							
	n.v.	v.				n.v.	v.										
Asphyxia	66	153	208	7	434	10	32	19		61	495	23·0	271 : 224	261	234	364	73
Asphyxia due to inhalation of foreign material		5	13		18	2	52	22		76	94	4·4	53 : 41	59	35	35	37
Asphyxia plus intracranial haemorrhage ..		22	34		56	3	23	10	1	37	93	4·3	55 : 38	48	45	67	72
Intracranial haemorrhage	11	18	28		57	40	226	61	1	328	385	18·0	232 : 153	296	89	150	42
Haemorhachis							20	4		24	24	1·1	15 : 9	20	4	0	0
Encephalitis							5	3	1	9	9	0·4	7 : 2	5	4	3	30
Other foetal traumata ..	1	3			4	1	4	3		8	12	0·56	10 : 2	9	3	1	8·3
Craniotomy	3	8	5		16						16	0·75	8 : 8	11	5	16	100
Congenital malformations	14	23	7		44	4	36	32		72	116	5·4	58 : 58	77	39	55	47
Erythroblastosis foetalis	1	6	6	1	14		7	22		29	43	2·0	20 : 23	14	29	20	47
Haemorhagic diathesis							2	1		3	3		2 : 1	2	1	0	
Congenital syphilis ..	1	10	2		13		4	3		7	20	0·93	10 : 10	15	5	5	25
Pneumonia		1	6		7	8	181	74		263	270	12·5	141 : 129	190	80	76	28
Umbilical sepsis ..							4	10		14	14	0·7	9 : 5	4	10	5	36
Incidental causes ..						1	67	36		104	104	4·8	49 : 55	68	36	43	41
Debility						106	124			230	230	9·3	129 : 101	230		186	80
Unspecified causes ..	56	74	29	2	161		24	5		29	190	8·9	105 : 85	154	36		
Various	2	2	3		7		12	10		22	29	1·35	12 : 17	16	13	9	31
Total	155	325	341	10	831	175	823	315	3	1,316	2,147	100·00	1,186 : 961	1,479	668	1,025	48

the stillbirth rate was much higher. I do not go into detail concerning the causes of asphyxia as was done in the remarkable paper of Russ and Strong (1946), for reasons which I shall mention later.

INTRACRANIAL HAEMORRHAGE. Second in frequency as a cause of death is intracranial haemorrhage. In my material it amounts to 18 per cent. of all perinatal deaths, and if we add the cases where haemorrhage was combined with asphyxia, it is 22·3 per cent. In Macgregor's survey it is still higher, amounting to 36·4 per cent. I would stress that a correct diagnosis of intracranial haemorrhage requires a very painstaking post-mortem technique, as artificial haemorrhage is readily produced.

Intracranial haemorrhage is mostly caused by birth stress, particularly if there is disproportion between the head of the foetus and the diameters of the pelvis. In cases of forceps delivery a direct injury by this instrument is often responsible. There is no doubt, however, that haemorrhage may be due solely to asphyxia or that the latter may at least contribute to it by raising the blood-pressure. It seems that ventricular haemorrhage in particular, which is mostly seen in premature foetuses, may be explained in this way. Be that as it may, another important contributary factor in the genesis of haemorrhage must be taken into consideration; it is the physiologically low coagulability of foetal blood as a result of hypoprothrombinaemia, probably due to lack of vitamin K. In one of the obstetric departments, where prophylactic treatment with a water-soluble preparation of vitamin K is consistently given to the prospective mothers, the incidence of deaths due to haemorrhage has been considerably reduced.

HAEMORHACHIS. Other traumatic lesions occurring during labour, such as disruption of the vertebral column, play an almost negligible role. This is somewhat different with haemorhachis. It is the routine in my department that, whenever the usual post-mortem technique fails to demonstrate any obvious cause of death, the vertebral canal is opened. By this, an extensive epidural haemorrhage may be found as the clear cause of death, particularly in premature infants who otherwise would receive a diagnosis of debility. This has been stressed by Hausbrandt (1938) in Germany; we came to the same conclusion before his communication was published but not during the period under discussion, so that we may have missed some cases of that kind. Recently, being more consistent in opening the vertebral canal, we have noticed that this condition is much more frequent than has generally been supposed.

CONGENITAL MALFORMATIONS. Whereas the causes so far discussed are all connected with birth stress, congenital malformations are generally referred to as the 'irreducible minimum,' because their occurrence is entirely independent of obstetric skill or ante-partum and postnatal care. It is remarkable, however, that their incidence in my material was considerably lower than in that of most British studies of the subject, being only 5·4 per cent. in contrast to 18·7 per cent. as given by Macgregor. For this difference no satisfactory explanation can be given. There is again some overlapping with other causes of death; for instance, a baby with a malformed heart may die not of this but of asphyxia or intracranial haemorrhage. We have, however, classified all cases having a malformation serious enough to be considered a potential cause of death under this heading, and not according to the actual cause of death. Thus the discrepancy cannot be simply explained by a different method of classification. The fact that the usual predominance of females in congenital malformations is not apparent in my material may be accidental.

ERYTHROBLASTOSIS FOETALIS. Erythroblastosis foetalis appears to be a much more frequent cause of perinatal death than was believed until recently. In addition to the three well-known manifestations, there are cases of prenatal death obviously due to familial erythroblastosis in which, however, the foetus shows no signs of the disease except some enlargement of the spleen, but maceration and autolysis renders microscopical diagnosis impossible. Moreover, consistent microscopical examination of foetuses, in which death was due to some other cause shows signs of erythroblastosis more frequently than would be suspected, and the correctness of the diagnosis can be confirmed by serological examination of the mother's blood for Rh-factor antibodies. We have introduced the term 'latent erythroblastosis' for such cases. We consider them very important, because, although erythroblastosis was not the actual cause of death, such findings may be a warning of the potential danger of later pregnancies, ending in typical erythroblastosis. Since we became aware of this fact the diagnosis has appeared considerably more frequently in our post-mortem records, and, therefore, the figure given in this synopsis may be rather too low.

HAEMORRHAGIC DIATHESIS. The rare finding of haemorrhagic diathesis in the newborn may be due either to erythroblastosis or to excessively severe hypoprothrombinaemia.

CONGENITAL SYPHILIS. The figure given here for congenital syphilis (less than 1 per cent.) might give the impression that this cause of perinatal death is practically negligible. I am afraid, however, that this is far from being correct. Earlier in the course of this study we perhaps depended too much on the macroscopical findings and dark-field examination of the liver. Later we learnt that in certain cases, chiefly macerated foetuses with at most a slight enlargement of the spleen, the dark-field examination sometimes gave a negative result whereas fairly numerous spirochaetes were demonstrable in tissue sections. Furthermore, there are cases of congenital syphilis in which the liver contains no spirochaetes, or very few, although these are found in numbers in some other organ such as the adrenal, the lungs, the thymus, or the pancreas.

We use Kanzler's method for staining spirochaetes in frozen or in single paraffin sections, and have found it entirely reliable. Since we made it a rule, to examine almost every macerated foetus in this way, the number of positive diagnoses has increased considerably. In the first five months of 1947 we have had seventeen, which is about 5·7 per cent. of all perinatal deaths. Among the latter there were thirty-one macerated foetuses, and thirteen of the positive cases (almost half) in this group. This, of course, may be due partly to an actual increase in syphilitic infection, for which the general decline in morality would sufficiently account. But I nevertheless believe that the improved method of diagnosis is at least partly responsible.

INFECTION. The further three items might as well be placed under the common heading of infection, as is done by Macgregor. For the cases placed under the term 'incidental causes' are mostly those of enteritis, or sepsis due to pyodermia, or otitis media. All three items together make 18 per cent., slightly less than with Macgregor's figure.

In my material the number of cases of umbilical sepsis is negligible. On the other hand pneumonia is the third most important cause of perinatal death, being outrated only by asphyxia and intracranial haemorrhage. There is little to be added to Macgregor's (1939) excellent paper on this subject. I am particularly in agreement with her statement that the diagnosis of pneumonia in the newborn cannot be made safely without microscopical examination. I would also call attention to the occurrence of pneumonia in stillborn foetuses, of which we saw seven instances. The problem of pathogenesis of this adnatal pneumonia is an intriguing one. There is no doubt that in asphyxia premature stimulation of the respiratory centre generally results in more or less massive aspiration of amniotic fluid, which at that time may have been infected. I have seen several cases in which the lungs of a stillborn asphyxiated foetus contained masses of bacteria. If the amniotic infection is of anaerobic gas-forming character there may be a precocious production of gas in the lungs, so that these float in water although the foetus was incontestably stillborn. But in such cases there would be no signs of inflammation, for this would have had no time to develop, as the foetus would have succumbed immediately to asphyxia. However, it may happen that infection of the amniotic fluid starts long before the interruption of the placental circulation induces breathing in the foetus. From recent experimental work it may be considered an established fact that long before labour sets in the foetus makes rudimentary breathing movements, which allow the amniotic fluid to enter the lungs. Infections of the amniotic fluid in the first stage of labour may thus have produced inflammatory changes by the time the child is born. Pending further experimental proof, this seems to be the best hypothetical explanation of the adnatal pneumonia.

DEBILITY. Under the item 'debility' are included cases in which no other cause of death could be established except prematurity. The latter may be assumed as a sole cause of death in non-viable immature infants or in those whose weight does not exceed 1,300 to 1,400 g. My colleague, Prof. Švejcar (Šikl et al., 1946) has given a very clear account of the ultimate causes of death due to prematurity. On the basis of the experimental work of Raiha, Hiltunen, and other Scandinavian authors, he comes to the conclusion that it is the incomplete development of cytochrome, the tissue respiratory ferment, that is to be blamed. Anyway, it is well known that newborn babies with a weight as low as 600 g. may sometimes be kept alive, but this requires painstaking care. Thus the conception of viability is relative, much depending on the equipment of the clinic. Unfortunately it cannot be said that our obstetrical clinics are quite up to date in this respect.

I have been surprised at the fact, that in Macgregor's paper the item 'debility' is entirely omitted. It seems that, with her, such cases have been included under the heading 'inconclusive autopsy.' However, we reserved the term 'causa incerta' chiefly for macerated foetuses in which autolysis of the organs precluded diagnosis. In addition there are a few cases born alive with a weight above 1,400 g. in which no obvious cause of death could be established.

Influence of prematurity. From all statistical surveys on this subject the far-reaching influence of prematurity on the neonatal death rate is obvious. Among the 39,000 births on which my statistics are based there were 4,902 premature, that is 12·5 per cent. (table 3). Of these, 480 were stillborn and 998 died in the neonatal period, which gives a total of 1,479 deaths. This makes a death rate of 301·7 per 1,000 of the premature. It is, however, to be stressed that 331 non-viable premature infants have been included. Among the 34,097 mature, however, there were only 669 deaths, thus the mortality was as low as 19·7 per 1,000, that is, more than fifteen times less than in the premature group. Thus the detrimental influence of prematurity comes out very markedly.

If we compare the percentages of the single causes of death in both groups, the differences appear to be rather slight except for the fact that in the immature group there is the additional item of debility. This, however, would give an entirely wrong idea of the importance of the causes of death in the immature group. Instead of comparing the same number of deaths in both groups, one must rather take as a basis the same number of births. Then the result is quite different. From fig. 2, the much greater suspectibility to any cause of death in the premature is clearly seen. Thus premature labour appears to be the prime problem in the prevention of perinatal mortality. To deal with the causes of premature labour, however, would much exceed my competence.

Collaboration of Clinician and Pathologist

In their remarkable paper on stillbirth and neonatal death, Evans and Smith (1946) make the following statement: 'In no other group is the close collaboration of pathologist and clinician so essential: without the clinician the autopsy findings cannot be interpreted; without a pathological examination opinion on the cause of death is often little better than guess-work.' As to the second half of this statement, I would refer to table 2. In the last two columns the conformity of the clinical

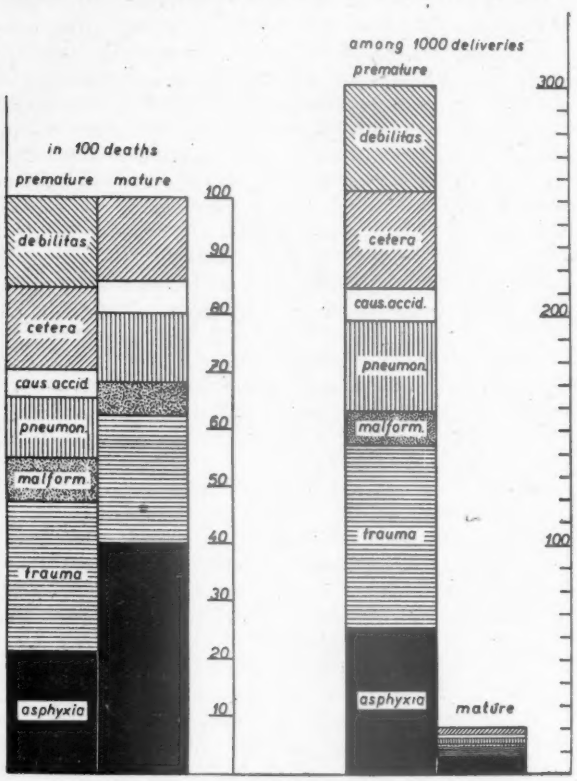

FIG. 2.—Distribution of causes of death.

diagnosis with the post-mortem findings is given in percentages. This varies between 0 and 80 per cent. A correct diagnosis is most often made in debility, as this is the most common diagnosis in neonatal death of the premature. A fairly close correspondence is also shown between asphyxia and intracranial haemorrhage. On the whole, however, one may imagine how different these statistics would look if they were based on clinical diagnosis alone.

The first half of the statement quoted is no less true. As a matter of fact, Evans and Smith were able, thanks to close collaboration between the clinician and the pathologist, to push the analysis of the causes of perinatal death much further than I could, in spite of my considerably larger material. I did my best to obtain such close collaboration, but the result was far short of expectations.

When, in 1941, I dealt with the subject for the first time, in a lecture delivered before the Czech Obstetrical Society in which I discussed my post-mortem experience of the previous year, it aroused much interest among the obstetricians, and it was decided then to go on with this work in the closest collaboration possible. This was actually done, and in 1943 a clinico-pathological symposion was held on the basis of the material of the previous two years. In this, the obstetricians took up the argument and gave a very thorough analysis of their fatal cases. The whole discussion was later published as a pamphlet, but in Czech only (Šikl et al., 1946).

Later on conditions took a turn for the worse. The Germans greatly reduced the medical staff of the clinics, and those remaining were too over-burdened to continue working on these lines. When the war was over many new medical men joined the clinics. They had not attended the preceding discussions and, in consequence, had little interest in the subject.

To overcome these difficulties I have recently compiled a rather elaborate questionnaire covering all data that may be helpful to the pathologist in his evaluation of post-mortem findings. It is meant to be filled in by the obstetrician and sent in along with the death certificate. I am doubtful how far this will work, but if it does I shall in course of time be able to give a much more adequate analysis of the causes of perinatal mortality than has been possible here.

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ON THE RELATIONSHIP BETWEEN MATERNAL CONDITIONS DURING PREGNANCY AND CONGENITAL MALFORMATIONS

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Introduction

Recently there has been an increased interest in the etiology of congenital malformations, and some fundamental clinical and experimental contributions to mammalian teratology have been made which indicate that developmental abnormalities may represent something more than unavoidable accidents of nature.

According to general theories, intra-uterine development is determined by the interaction between inherited principles in the foetus and environmental conditions which surround and act upon it. The question has repeatedly arisen as to whether congenital malformations are due mainly to inherited factors present in the germ cell or whether some of them may be considered as possible products of environmental influences. Most studies in human genetics have, until recently, not taken into consideration the full significance of environmental factors in the etiology of congenital malformations, although this question has been discussed in the past. It is thus remarkable that as long ago as 1902 Ballantyne made the following statement: ' There is good reason for believing that malformations and monstrosities are the product of morbid agents acting during the embryonic period.' Since that time considerable research has been done in this field, and we are now able to distinguish several environmental factors which, besides the genetic ones, play a certain role in the pathogenesis of congenital abnormalities.

A. Age and Parity of the Mother

These are two environmental factors which lend themselves readily to statistical investigations. For instance, it has been established by a large number of observers that mongolian idiocy is closely associated with advanced maternal age (Shuttleworth, 1909; Shrubshall, 1925; Penrose, 1932; Lahdensuu, 1937; Bleyer, 1938; Ingalls, 1947). The theory has, therefore, been advanced that mongolism is to some extent a result of changes of foetal environment due to this state. Advanced age of the mother has also been shown to be a factor in other congenital malformations, such as anencephaly, spina bifida, and congenital hydrocephaly (Malpas, 1937; Penrose, 1946a). In one series of 570 families with children showing various congenital abnormalities, Murphy (1936) reported that the mean maternal age at the time of birth of the first malformed child was 28·4 years, the corresponding age at the birth of the first normal child being 23 years.

Some authors have noticed that certain abnormalities appear more often in the first-born than in subsequent pregnancies. Still (1927), for instance, reported the well-known fact that a large proportion of children with pyloric stenosis are first-born, and suggested that the same is probably true for some other abnormalities. Primogeniture also is shown to be of possible etiological significance with regard to anencephaly, spina bifida, and congenital hydrocephaly (Malpas, 1937; Penrose, 1946a). On the other hand, some malformations tend to occur more often in later born children than in earlier siblings. Certain forms of mental deficiency, most notably mongolian idiocy, seem to come into this category (Penrose, 1934). Malpas (1937) reported in a study of 294 children with various congenital malformations born at the Liverpool Maternity Hospital that 70 per cent. of the children with cleft palate and harelip were born to multiparae in contrast to an average of multiparae in the whole hospital population of 54 per cent. In a similar study of 582 malformed children in whom hydrocephaly and spina bifida were represented in nearly one-half of the cases, Murphy and Mazer (1935) concluded that congenital abnormalities occurred more frequently in later than in earlier pregnancies.

B. Maternal Infectious Diseases

It has long been recognized that maternal infectious diseases during pregnancy may occasionally be transmitted to the foetus. Foetal variola, for instance, had been described already in 1702 by

Düttel. Similar observations on the intra-uterine transmission of malaria, yellow fever, and relapsing fever have been made in the past by Russell (1800), Finlay (1894), and Albrecht (1884). It has also been noticed that severe maternal infections during pregnancy are likely to cause death of the foetus. Thus, observations during the severe epidemic of influenza in 1918 indicated that about 30 to 50 per cent. of the mothers who contracted this disease during pregnancy lost their babies as abortions, stillbirths, or neonatal deaths (Bland, 1919; Harris, 1919).

In the past, some authors observed that infants of women who had suffered from infectious diseases during pregnancy sometimes exhibited anomalies of structure or actual malformations. Maternal syphilis is one of the first diseases to which has been attributed a teratogenic effect on the foetus. Thus Fournier (1898), in an extensive paper on syphilis, stated that the disease in pregnant women might cause malformations of the foetus such as harelip, cleft palate, spina bifida, and congenital heart disease. In recent times, some authors, especially in France, have attributed to this 'théorie syphilitique' an important role in the etiology of congenital abnormalities (Paucot et al., 1946). They reported a series of 109 children with congenital malformations, and considered that syphilis was a causative factor in 45 per cent. of the cases. There was, however, no information as to the incidence of this disease among mothers with normal children. Several authors, on the other hand, have not been able to establish any significant relationship between syphilis and congenital malformations (Clark, 1932; Murphy, 1937; Dogramaci and Green, 1947; and others).

The rare occurrence of congenital tuberculosis has been known since Charrin (1874) first published a case. Since then some authors have described solitary cases and have pointed out a possible relationship between maternal tuberculosis and certain congenital malformations in the foetus, such as deformities of the limbs, congenital heart disease, and actual monstrosities (Sarwey, 1892;—Hanot, 1896; Kleim, 1899; Ballantyne, 1899, 1902). In recent times Murphy (1947) reported a series, comprising 109 malformed children, among whose parents pulmonary tuberculosis was detected in sixteen instances.

A supposedly benign disease, previously considered too slight in its effect on the mother to cause any influence on foetal health, suddenly assumed a more serious significance when Gregg (1941) reported the relationship between rubella in pregnant women and congenital malformations in the foetus. As evidence accumulated, a number of defects such as microcephaly, cataract, congenital heart disease, and deafness appeared to be directly attributed to the occurrence of rubella during pregnancy. Up to the present time about six hundred cases of congenital malformations associated with maternal rubella have been published. Extensive surveys on this subject have recently been given by Swan and Tostevin (1946), Aycock and Ingalls (1946), Murphy (1947), and Wesselhoeft (1947). Swan and his collaborators stated that when a woman contracts rubella within the first two months of pregnancy the chances of her giving birth to malformed children are about 100 per cent., and in the third month they are about 50 per cent. It is still possible that the child will present abnormalities even if rubella is contracted after the first trimester of pregnancy. There are, however, several observations suggesting that rubella during pregnancy is not associated with congenital malformations of the foetus as frequently as was thought. In America, Fox and Bortin (1946) reported that among eleven women who contracted rubella during pregnancy, nine being during the first four months of gestation, only one gave birth to a malformed child. In a similar study, Aycock and Ingalls (1946) observed that one in four pregnancies resulted in a defective child. Clayton-Jones (1947) has made enquiries in schools for deaf children in Manchester and has discovered a history of maternal rubella during pregnancy in about 11 per cent. of the cases. The time of the birth of these children corresponded with the large epidemic in 1940 of rubella in Manchester. A second epidemic in 1941 did not show a corresponding rise in the incidence of congenital malformations. Recently Grönvall and Selander (1948) have collected data about the occurrence of various virus diseases during pregnancy among 24,519 women in Sweden. In twenty-six cases a history of rubella, mostly within the first four months of gestation, was obtained. However, only one mother gave birth to a malformed child.

The possibility has been discussed whether the originally reported disease in Australia really was rubella or whether it was an unusually severe form of the disease (Parsons, 1946, and others). Although no definite answer has so far been obtained upon this question, the combined observations in this field indicate that environmental factors are involved in the etiology of the prenatal 'rubella syndrome.'

The established relationship between rubella and congenital malformations has given rise to the question as to what extent acute infectious diseases in general may be a primary cause in the etiology of these abnormalities. However, investigations dealing with this subject are very few. Albaugh (1945) described a child with congenital cataract, whose mother had contracted measles during pregnancy. Solitary cases of actual malformations in association with maternal measles have been observed by Swan and Tostevin (1946) and by Dogramaci and Green (1947). The former authors also reported two cases of malformed children, whose mothers had had varicella during pregnancy. A similar case has been published by Prendergast (1946). On the other hand, Grönvall and Selander (1948) did not find malformations among thirty-one children whose mothers had suffered from measles or varicella when pregnant. Observations pointing

out a certain relationship between some other maternal virus diseases, such as poliomyelitis and mumps, and congenital malformations of the foetus, have been made by Aycock and Ingalls (1946), by Swan and Tostevin (1946), and by Grönvall and Selander (1948). Recently some authors have drawn attention to maternal toxoplasmosis as a possible cause of congenital malformations (Wolf et al., 1941; Wagener, 1944; Magnusson, 1947; Warkany, 1947).

C. Nutritional Condition of the Mother

It has long been known that foetal development in utero is particularly related to the nutritional condition of the mother. In the last world war an unusually high incidence of premature births associated with maternal starvation during pregnancy was reported by Antinov (1947) and by Smith (1947). Some authors have observed a relatively high incidence of dietary deficiency during pregnancy among mothers of malformed children (Murphy and DePlanter Bowes, 1939; Burke et al., 1943). That specific insufficiencies in maternal nutrition may produce congenital defects in the offspring is shown in the extensive experimental work by Warkany and his collaborators (1941-44). They noticed that malformations such as cleft palate and various defects of the limbs occurred frequently among the litters born to rats kept on a riboflavin-deficient diet before the first two weeks of gestation. These results have later been confirmed by Noback and Kupperman (1944). Lack of vitamin A and D in rats during pregnancy has also been associated with the occurrence of congenital malformations in their progeny (Hale, 1933, 1935; Warkany, 1943). It does not follow, however, that these experimental results obtained in animals necessarily apply to man. In fact, Brzezinski et al. (1947) did not observe an increased incidence of malformations in the children of 326 mothers who had suffered from riboflavin deficiency during pregnancy.

D. Mechanical Factors

Mechanical factors or an abnormal foetal implantation have also been suggested as possible causes of congenital malformations. von Winckel (1902) and Mall (1908) reported an unduly high incidence of malformed children in association with ectopic pregnancy. Later investigations, on the other hand, have not been able to show any significant relationship between these two conditions (Dehler, 1924; Malpas, 1937). Amniotic bands have also been considered as a cause of some congenital abnormalities (Grosser, 1938), but no satisfactory proof of their significance has been made. Browne (1934) has suggested that various congenital deformities, especially those of the limbs, could be caused by an abnormal position of the foetus in utero or by an increased intra-uterine pressure. The occasional occurrence of foetal malformations in association with placenta praevia may be of some significance. In a survey of 4,446 children born to mothers with placenta praevia, Greenhill (1939) reported that the incidence of foetal abnormalities was approximately three times higher than under ordinary conditions. Before attaching importance to this disorder as a primary cause of congenital malformations, it is necessary to emphasize that according to Penrose (1939) hereditary factors seem to play a part in the etiology of placenta praevia.

Schröder (1938) reported that a high proportion, 27 per cent., of mothers of mongolian idiots were found to have a retroflexed or prolapsed uterus, while only 5·5 per cent. of women with normal children revealed such abnormalities. Goldstein and Murphy (1929b) on the other hand, did not observe a significant correlation between maternal pelvic disorders and foetal malformations.

E. X-ray and Radium Irradiation

In 1907 von Hippel and Pagenstecher observed that x-ray irradiation of pregnant animals could cause malformations in the offspring. Later on, x-ray and radium irradiation were used in the experimental production of malformations in animals by Hanson (1923), Bagg and Little (1924), Murphy and Renyi (1930), Hertwig (1939), Raynaud and Frilley (1943), and Warkany and Schraffenberger (1947). Two different methods have been employed. Experimental mutations can be induced by irradiating the sex glands of mature females whereupon malformations develop in the subsequent generation. Alternatively, developmental defects can be provoked by direct irradiation of the foetus itself in utero. The last method was used by Warkany and Schraffenberger in a large series of rats, and in a large proportion of the offspring marked skeletal abnormalities were found, such as cleft palate, clubbed feet, shortening of mandibles, and defects of the skull. An interesting observation was that the stage of pregnancy at which the irradiation was carried out had a decisive influence upon the type of malformation produced. Therapeutic x-ray and radium irradiation of the human pelvis are also very likely to cause malformations of the foetus (Aschenheim, 1920; Zappert, 1926; Murphy, 1928; Goldstein and Murphy, 1929a). Murphy reported a study of 106 women who had been exposed to x-ray and radium irradiation during pregnancy for various reasons; seventy-five of them gave birth to children at term, and thirty-eight of these were abnormal. Microcephaly is reported as the most usual foetal abnormality due to irradiation of the mother during pregnancy.

F. Various Foetal Environmental Factors

Our knowledge of the significance of other environmental factors in the etiology of congenital malformations is very incomplete. The dependence of reproduction upon proper co-ordinated hormonal influences has been stressed in the past. Duncan (1883) and Whitridge Williams (1909) were among

the first who noticed a high tendency of stillbirths among diabetic mothers, and a certain relationship between this disease and congenital malformations has been observed by Lecorché (1885), Skipper (1933), and by Hurwitz and Irving (1937).

The possible influence of certain chemical factors upon the reproductive ability has been discussed by various authors. For instance, frequent abortions have been noticed among women working in lead industries (Paul, 1860), and foetal malformations including skeletal deformities and heart defects have also been attributed to maternal lead poisoning (Rennert, 1881; Dogramaci and Green, 1947).

Congenital malformations have also been attributed to alcoholism in the mother (Fournier, 1898; Ballantyne, 1902; Margouliss, 1940), but no definite proof has so far been given of such a relationship.

Finally, recent observations have shown an unusually high incidence of congenital malformations in children with erythroblastosis (Weber and Scholtz, 1939; Javert, 1942; Wiener, 1947). Javert described a series of forty-seven infants with erythroblastosis of whom ten revealed congenital malformations.

The whole matter may be summarized as follows. Various observations have shown that environmental principles play an important part in the etiology of congenital malformations. Foetal abnormalities result, but not of any characteristic type in relation to the various causes. The most important factor appears to be the stage at which foetal development is disturbed. Due to the lack of specificity of teratogenic characteristics, malformations caused by environmental agents may simulate abnormalities of genetical origin.

These observations in mammals have been supported by experiments in lower animals (Stockard, 1910, 1920) but our knowledge of the whole subject is still imperfect.

Present Investigation

The influence of maternal disorders during pregnancy on foetal development can be studied in two ways. The method usually employed is to select children with congenital malformations and to question the mothers retrospectively as to the state of their health during pregnancy. However, fallacies can easily arise in such an enquiry as it depends so largely on the subjective interpretation and memory of the mother; moreover, it lacks control.

A more reliable method is to approach the problem from the other direction with a careful review of the obstetric history of a large series of women and to follow this by a study of any foetal abnormalities which might be related.

This was the principle adopted in a recent investigation carried out at the Obstetric Hospital and the Paediatric Department, University College Hospital in London. Its aim has been to obtain by means of comparative studies a further insight into the relationship between maternal conditions during pregnancy and congenital malformations. For this purpose data concerning the health of mothers who subsequently gave birth to malformed children have been collected from the antenatal records. This has been possible because the majority of women who attend the hospital for delivery have been followed up at the antenatal clinic from their early pregnancy. The antenatal records contain detailed information of the health of the mothers before and during pregnancy (Browne, 1946). Since 1945 the records contain a special clause referring to acute infectious diseases during pregnancy.

When interpreting the possible association between various disorders during pregnancy and congenital malformations, it has seemed necessary to investigate the occurrence of corresponding disorders under ordinary conditions. As controls 200 women were chosen at random, who during the same period gave birth to normal children in the same Department.

In comparing the results obtained in the two groups current statistical formulae have been employed (see Appendix).

Results

Information has been collected about seventy-three malformed children who were born during the years 1945-48 in this hospital. During this period the total number of deliveries amounted to 3,593, showing an incidence of children with malformations of about 2 per cent., a figure which corresponds on the whole with observations made in other hospitals (Naujoks, 1938; Malpas, 1937; Tholen, 1946).

It is well known that congenital malformations are often multiple. For the sake of clarity the cases under consideration have been classified under the chief malformations present (table 1).

It will be seen that malformations of the central nervous system were the most common (eighteen cases). Deformities of the limbs came next in frequency and consisted mainly of clubbed feet and solitary cases of anomalies of fingers and toes. A miscellaneous group has been included consisting mainly of deformities of the visceral organs and abnormalities of the skin.

Maternal age. The mean age of the mothers of malformed children was 28·6 years, the corresponding figure for the mothers in the control group being 26·5 years. The value for t (5·0) gives a significantly positive correlation between advanced maternal age and the occurrence of congenital malformations in these studies.

TABLE 1

AGE AND PARITY OF SEVENTY-THREE MOTHERS WITH MALFORMED CHILDREN AND OF TWO HUNDRED MOTHERS WITH NORMAL CHILDREN

	Chief malformations of the children	No. of cases	Maternal age						Parity				
			15-19	20-24	25-29	30-34	35-39	40-44	0	1	2	3	4-5
Age and parity of 73 mothers with malformed children.	Anencephaly	12	—	4	6	2	—	—	8	2	1	—	1
	Spina bifida	6	—	1	2	2	1	—	5	—	1	—	—
	Mongolism	4	—	—	—	1	2	1	2	1	—	1	—
	Deformities of the limbs	13	—	8	1	1	3	—	10	2	—	1	—
	Congenital heart disease	11	2	1	3	2	1	2	9	—	—	1	1
	Hare lip and cleft palate	5	—	1	1	1	1	1	4	—	—	—	1
	Hypospadias	4	—	—	2	1	1	—	1	3	—	—	—
	Miscellaneous	18	1	4	5	2	6	—	13	2	1	—	2
	Total ..	73	3	19	20	12	15	4	52	10	3	3	5
Age and parity of 200 mothers with normal children.	Total ..	200	11	83	59	34	9	4	152	40	5	1	2

Parity. Fifty-two of the seventy-three children with malformations were firstborn. Among the 200 normal children the corresponding number was one hundred and fifty-two. A comparison between these two ratios shows that there was a significantly higher incidence of multiparae among the mothers in the former group ($t = 2 \cdot 5$).

Previous abortions. Fourteen (19·1 per cent.) of the mothers who gave birth to malformed children had had previous abortions. In the control group only fifteen mothers (7·5 per cent.) gave a similar history. The difference between the two ratios is significant ($Chi = 2 \cdot 9$). With regard to the menstrual history no deviation from normal conditions was detected among the mothers who subsequently gave birth to malformed children.

The Health of the Mothers during Pregnancy

It has already been mentioned that the majority of the mothers have been carefully followed up at the antenatal clinic from their early pregnancy. Reference is now made to the question whether there are maternal disorders during pregnancy predisposing or at any rate preceding the occurrence of foetal malformations.

In all cases the general condition of the mothers during pregnancy was satisfactory, and no clinical signs of undernourishment or vitamin deficiency could be detected. None of the mothers revealed any sign of congenital malformations. There were no cases of psychical disturbances during pregnancy, which supports the view that the importance of these disturbances in the etiology of congenital malformations has in the past been overestimated.

Ante-partum haemorrhage. Fifteen of the mothers with malformed children (20·5 per cent.) had had gestational bleeding, some of them on several occasions. In the control group nine mothers (4·3 per cent.) gave a history of ante-partum haemorrhage, showing a significantly higher incidence of this disturbance in the former group ($Chi = 4 \cdot 4$). During the last ten years the incidence of gestational bleeding for the whole hospital population has been 3·9 per cent.

Toxaemia. In the Obstetric Hospital, University College Hospital, a blood pressure of 120/80 mm.Hg. is considered the upper limit of the normal, irrespective of the age of the patient, and a blood pressure exceeding this level is interpreted as a sign of toxaemia. Various types of toxaemia during pregnancy occurred in thirty-eight (53·6 per cent.) of the seventy-three mothers who bore children with malformations. In only one case was albumin detected in the urine. The corresponding incidence of toxaemia in the control group was slightly less (45·1 per cent.). The difference, however, is not significant ($Chi = 1 \cdot 0$). During the last ten years toxaemia, according to this very strict definition, has been observed in about 50 per cent. of the whole hospital population. Thus, this disturbance does not seem to be especially commonly associated with the occurrence of foetal malformations in these studies. In this connexion it may be mentioned that Naujoks (1938) reported a relatively high incidence of toxaemia during pregnancy among mothers who subsequently gave birth to malformed children.

Various diseases during pregnancy. Detailed information on the occurrence of morbid states in the mothers has been gathered from the antenatal records. With regard to acute diseases, only those which occurred within the first five months of

TABLE 2

MORBID STATES DURING PREGNANCY OF THIRTY-THREE MOTHERS WITH MALFORMED CHILDREN

Case no.	Maternal age	Parity	Morbid state of the mother	Stage of pregnancy in weeks	Chief malformation of the children
			ACUTE INFECTIOUS DISEASE :		
1	22	0	Influenza, ' cold '	8	Naevus
2	25	0	" "	9	"
3	21	0	" "	10	Congenital heart disease
4	39	3	" "	10	" " "
5	22	0	" "	11	Naevus
6	30	0	Pneumonia	12	Spina bifida
7	26	0	Sore throats	4	Naevus
8	24	1	" "	4	Clubbed feet
9	24	0	Cough (bronchitis)	4	Defect of diaphragm
10	26	0	" "	12	Anomaly of kidneys
11	29	0	" "	12	Spina bifida
12	26	0	Pyelitis	4	Congenital heart disease
			CHRONIC INFECTIOUS DISEASE :		
13	37	0	Inactive pulmonary tuberculosis		Naevus
14	36	0	" " "		Clubbed feet
15	23	1	" " "		Hypospadias
16	25	0	" " "		Naevus
17	36	1	Chronic bronchitis		Anomaly of kidney
			MISCELLANEOUS :		
18	35	2	Jaundice		Atresia of rectum
19	34	1	X-ray irradiation of pelvis		Hypospadias
20	34	1	Diabetes		Defect of hand
21	30	1	Thyrotoxicosis		Anencephaly
22	41	1	Anaemia gravis		Congenital heart disease
23	26	0	" "	See text	Anencephaly
24	24	0	Mitral stenosis		Clubbed feet
25	18	0	" "		Congenital heart disease
26	41	0	" "		Mongolism
27	26	0	" "		"
28	30	0	" "		Cleft palate
29	40	4	Hepatomegaly		" "
30	25	0	Uterus duplex		Encephalocele
31	37	3	Cervix uteri amputated		Clubbed feet
32	26	0	Cervical polyp		Spina bifida
33	23	0	Rh negative		Anencephaly

gestation have been included. According to the present state of knowledge it is very unlikely that injurious agents may cause foetal malformations after that time.

Among the seventy-three mothers of malformed children, various disorders during pregnancy were observed in thirty-three cases (45·2 per cent.). In table 2 these cases have been separated into three groups.

The first group in table 2 consists of twelve cases where the mothers had suffered from acute infectious diseases. It is noteworthy that the infections occurred in all cases within the first three months of pregnancy. In the second group are collected four cases of inactive pulmonary tuberculosis and one case of chronic bronchitis. In these the clinical findings remained on the whole unchanged throughout pregnancy. There was no case of syphilis among the mothers. Over the same period a positive Wassermann reaction was observed in 0·97 per cent. of the whole hospital population.

The miscellaneous group consists of sixteen cases with various morbid conditions. Case 18 was that of a woman who, four weeks before conception, had had a blood transfusion to overcome anaemia caused by an abortion. In the fourth week of gestation jaundice was diagnosed. This may have been due to the transfusion (she was Rh-negative), but the possibility of the jaundice being of infectious origin cannot be excluded. One mother (No. 19) had been submitted to x-ray irradiation for amenorrhoea in another hospital on several occasions six years before the birth of her present child. One year after the last treatment she gave birth to a microcephalic child. In two cases (Nos. 22 and 23) severe anaemia was present throughout the pregnancy, haemoglobin

TABLE 3

MORBID STATES DURING PREGNANCY OF TWENTY-NINE MOTHERS WITH NORMAL CHILDREN

Morbid state of the mother	No. of cases	Stage of pregnancy in weeks
ACUTE INFECTIOUS DISEASE		
Influenza, ' cold ' ..	3	15, 16, 20
Cough (bronchitis) ..	4	8, 13, 13, 16
Sore throats ..	2	4, 12
CHRONIC INFECTIOUS DISEASE		
Inactive pulmonary tuberculosis	6	See text
MISCELLANEOUS		
Mitral stenosis	7	
Placenta praevia ..	3	
Diabetes	1	
Thyrotoxicosis	1	
Ulcus duodeni	1	
Rh negative	1	
Total	29	

values varying between 40 and 50 per cent. In addition, two mothers revealed a slight degree of anaemia; the remainder had haemoglobin values exceeding 70 per cent. In one case (No. 33) the mother was Rh-negative, her child and husband being Rh-positive.

Five mothers had clinical signs of mitral stenosis, apparently of rheumatic origin. Hepatomegaly of uncertain origin and persisting throughout pregnancy was diagnosed in one case (No. 29). Only in three cases were abnormalities of the generative organs observed (Nos. 30-32). There were no cases of ectopic gestation or placenta praevia among the mothers with malformed children. During the same period ectopic gestation occurred on fifteen occasions in the whole hospital population. In two cases version of the foetus was performed at the end of pregnancy; in the remaining cases the intra-uterine position of the foetus was normal. In the control group version was done in three instances.

Various types of foetal malformations were seen, and quite obviously no characteristic abnormality could be correlated with any particular group of maternal disorder. Abnormalities of the skin (naevi) seemed, however, to be confined to the group in which infections had occurred in the mother during pregnancy.

In table 3 are collected data about the corresponding occurrence of morbid states among the two hundred mothers who gave birth to normal children. Twenty-nine (14·5 per cent.) of the mothers had a history of various disorders during pregnancy. There were nine cases of acute infectious diseases but only in three mothers did these occur within the first trimester of pregnancy. The group of chronic infectious diseases comprises six cases of inactive pulmonary tuberculosis. In the third group are included seven cases of mitral stenosis, apparently of rheumatic origin. Placenta praevia occurred in three instances. No cases of ectopic gestation were observed, and no abnormalities of the generative organs. There were no cases of severe anaemia (haemoglobin value below 60 per cent.). One mother was Rh-negative, her child and husband being Rh-positive. Examination of the blood for a Rh factor was carried out in thirty-two mothers with malformed children and in 102 cases in the

TABLE 4

SEVENTY-THREE MOTHERS WITH MALFORMED CHILDREN AND TWO HUNDRED MOTHERS WITH NORMAL CHILDREN

	Morbid state of the mother during pregnancy	No. of cases	Maternal age						Parity				
			15-19	20-24	25-29	30-34	35-39	40-44	0	1	2	3	4-5
73 mothers with malformed children.	Acute infectious disease	12	—	5	5	1	1	—	10	1	—	1	—
	Chronic infectious disease	5	—	1	1	—	3	—	3	2	—	—	—
	Miscellaneous	16	1	2	4	4	2	3	9	4	1	1	1
	Disorder total ..	33	1	8	10	5	6	3	22	7	1	2	1
	No disorder ..	40	2	11	10	7	9	1	30	3	2	1	4
	Total	73	3	19	20	12	15	4	52	10	3	3	5
200 mothers with normal children.	Acute infectious disease ..	9	3	3	2	—	1	—	8	1	—	—	—
	Chronic infectious disease	6	—	4	—	1	1	—	5	1	—	—	—
	Miscellaneous	14	—	5	2	4	2	1	8	4	—	—	2
	Disorder total ..	29	3	12	4	5	4	1	21	6	—	—	2
	No disorder ..	171	8	71	55	29	5	3	131	34	5	1	—
	Total	200	11	83	59	34	9	4	152	40	5	1	2

control group. The number of Rh-positive mothers was twenty-eight and eighty-six respectively.

The main results of this investigation are compared in table 4. It will be seen that various morbid states during early pregnancy occurred more often among the mothers with malformed children. The difference between these two total ratios is highly significant (Chi = 6·3). Taking the three groups of disorders separately, there was a positive correlation between the occurrence of acute and chronic infectious diseases during pregnancy and foetal malformations (Chi = 4·1 and 2·2 respectively). The incidence of disorders included in the miscellaneous group was significantly higher among the mothers with malformed children (Chi = 5·4).

The mean age was slightly higher among the mothers with malformed than among those with normal children. The difference, however, was not significant (t = 1·4). Also with regard to the maternal age in the three subgroups no significant difference was observed, the value for t being 0·9, 1·6, and 0·5 respectively. The parity of the mothers with malformed and with normal children did not show any significant difference. The value for t, calculated for the two main groups, was 0·2.

Discussion

The investigations support the view that advanced maternal age and multiparity are two factors involved in the etiology of congenital malformations. It is difficult to interpret this relationship, but the relatively high incidence of malformed children in these cases is probably an expression of a diminished maternal reproductive ability perhaps of hormonal origin. The possibility must also be considered that this maternal disability is to some extent associated with constitutional characteristics predisposing to the production of malformed children. The high incidence of previous abortions among mothers with malformed children supports this possibility.

It is noteworthy that ante-partum haemorrhage preceded the birth of malformed children much more often than in the case of normal children. Ingalls and Davies (1947), who observed an unduly high incidence of bleeding during pregnancy in mothers who subsequently gave birth to mongolian imbeciles, considered the bleeding a causative factor of this foetal abnormality. It is, however, possible that the occurrence of ante-partum haemorrhage in association with abnormalities of the foetus is an expression of an incompatibility between mother and foetus, and this incompatibility might cause the tendency to abort. If this were true the bleeding would be a secondary phenomenon, rather than a primary cause of the foetal malformation. In this connexion it may be mentioned that Kalmus (1947) observed a positive correlation between ante-partum haemorrhage and advanced maternal age. It is, therefore, likely that the high incidence of gestational bleeding among mothers with malformed children in the present studies may be due partly to their relatively advanced age.

The observations have shown an abnormally high incidence of various morbid states during the early pregnancy among the mothers who gave birth to malformed children. The possibility must, therefore, be considered that these disorders are in some way involved in the etiology of the foetal malformations. It is noteworthy that there was no difference in age and parity in the two groups of mothers who had revealed various morbid symptoms during their pregnancy. This speaks in favour of the possibility that maternal disorders may act independently of other environmental principles that play a part in the causation of foetal abnormalities. It is significant that in the mothers with malformed children the infections occurred within the first three months of pregnancy, whereas in the control group they were generally observed after that time.

Any ideas of the mode of action of the various factors mentioned must for the moment remain entirely speculative. With regard to the teratogenic effect of certain virus diseases, such as rubella, the possibility of a direct action of the virus upon the growing embryo has been discussed (Swan and Tostevin, 1946; Morhardt, 1946; and others). This assumption is based upon the experimental observation that viruses have a special predilection for embryonic tissues.

The possibility must also be considered that an antigen-antibody reaction may have a harmful effect on the foetus. There is little doubt, for instance, that erythroblastosis foetalis is due to a blood incompatibility between the mother and her infant. The discovery of the Rh factor as a main cause of this disorder has given rise to the speculation that other abnormalities of the foetus may be connected with other incompatibilities of the blood (Penrose, 1946b, 1946c; Wiener, 1947). On the basis of this theory, it is possible that antibodies produced by various morbid states in the mother may interfere with the proper differentiation of the foetus during an early stage of pregnancy.

Summary

The aim of this work was to investigate, by means of comparative studies, the relationship between maternal conditions during pregnancy and congenital malformations of the foetus. For this purpose detailed data were collected from the antenatal records of seventy-three mothers who gave birth to malformed children at the Obstetric Hospital, University College Hospital, London, between the years 1945-48. Two hundred mothers who gave birth to normal children at the same hospital during this period were used as controls. The following main results have been obtained.

The mean age of the mothers with malformed children was significantly higher than the maternal age in the control group. There was also a positive correlation between multiparity and the occurrence of foetal malformations.

Fifteen, or 19·5 per cent., of the mothers with malformed children had had previous abortions, the corresponding incidence in the control group being 7·5 per cent.

The nutritional condition of the mothers during pregnancy was satisfactory in all cases, and no clinical signs of vitamin deficiency were observed.

Ante-partum haemorrhage occurred more often in pregnancies resulting in the birth of malformed children. The incidence of this disorder was 20·5 per cent. and 4·3 per cent. respectively in the two groups.

With regard to the occurrence of toxaemia during pregnancy, no significant difference was established between the mothers in the two groups.

Apart from ante-partum haemorrhage and toxaemia, various morbid states were observed during early pregnancy in 42·5 per cent. of the mothers who gave birth to malformed children. Acute infectious diseases occurred in twelve cases, all within the first three months of gestation. Of the mothers with normal children, a total of 14·5 per cent. had a corresponding history of various disorders during their pregnancy. There were nine cases of acute infectious diseases, of which, however, six occurred after the first three months of gestation.

The relatively high incidence of various morbid states during pregnancy among mothers with malformed children has led to the assumption that these states may be involved in the pathogenesis of foetal malformations.

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Appendix

Current statistical formulae have been employed for the interpretation of the results (Fisher, 1936).

The significance of a difference has been determined according to the following formula:

$$t = \frac{M_1 - M_2}{\sqrt{V}}$$

where M_1 and M_2 are the means of two series and V is the variance of this difference.

The value of Chi has been calculated according to the 2 by 2 tables as follows:

$$\text{Chi} = (xw - yz)\sqrt{\frac{(x+y+w+z)}{(x+z)\,(y+w)\,(x+y)\,(w+z)}}$$

where the numbers observed in the four classes are:

$$\begin{array}{c|c} x & y \\ \hline z & w \end{array}$$

A value of t or Chi of 2·5 or more is considered statistically significant.

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THE RADIOLOGY OF INTESTINAL OBSTRUCTION IN CHILDREN AND INFANTS

BY

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Introduction

Organic intestinal obstruction is often late in producing marked abdominal signs, and diagnosis tends to be delayed. Although nothing can replace a careful record of the history and thorough clinical examination, any further diagnostic aid which is safe, simple, and effective is welcome in doubtful cases.

Flat x-ray investigation of the abdomen in cases of suspected obstruction in adults and children has been used for some years, but not as extensively as it might be. Every clinician is anxious to avoid performing an unnecessary laparotomy, particularly in an ill child. Consequently there is a tendency to keep cases of suspected obstruction under clinical observation until a diagnosis can be made. This may mean that the child becomes acutely obstructed. If there is any investigation that will enable a diagnosis to be made at an earlier stage, that method should be adopted in all cases of doubt. Flat radiographs of the abdomen can give such information. There are, however, pitfalls in this form of investigation, and it is thought that the publication of some cases illustrating the scope and limitations of the method, may be of some value to paediatricians.

Radiological Investigation in Intestinal Obstruction

The diagnosis rests on the interpretation of abdominal gas shadows. Gas is normally present in the large bowel, and in infants commonly in the small bowel too. Over the age of three years gas is present in the small bowel, but unless some disorder of motility intervenes, and that disorder may be of a very minor nature, the gas is usually finely divided and intermixed with the fluid contents of the small bowel and rarely casts any shadow on a radiograph. Normally the contents of the small bowel are propelled towards the large bowel, and stasis does not occur. Thus, if gas is present in the small bowel, it will under normal conditions also be present in the large bowel. If gas is present in the small bowel and not in the large, if that part of the small bowel in which it is present is distended, and if in addition the existence of stasis in the small bowel can be demonstrated, then it can be deduced that some form of mechanical obstruction is preventing the onward passage of that gas. Obstruction of the large bowel can be diagnosed in a similar manner.

One of the most frequent causes of obstruction in infancy and early childhood is intussusception. Diagnosis is often difficult, especially in those cases where blood in the stools is a late symptom. Hellmer (1943) published a series of 110 cases of intussusception investigated and diagnosed by means of a barium enema. However, in a shocked child barium enema is not a procedure to be undertaken lightly; it will not improve the child's condition, and in any case is unlikely to demonstrate an ileo-ileal intussusception or a small-bowel obstruction from any other cause. Oral barium is to be avoided. The radiological procedure of taking straight films of the abdomen, however, is simple, in no way upsets the child, and, in a case of obstruction, whatever the cause may be, gives positive evidence in most cases.

Radiologically the various parts of the small and large bowel can be recognized with relative certainty. The upper part of the small bowel lies mainly in the upper abdomen and to the left side, and shows the mucosal folds or valvulae conniventes of the jejunum close together. The mid small bowel lies mainly in the umbilical region, and the mucosal folds are rather more widely spaced. The lower part of the small bowel lies mainly in the right flank and pelvis and shows the smooth walls of the ileum devoid of mucosal folds. The caecum and ascending colon lie in the right flank, the transverse colon crosses the upper abdomen, and the descending colon occupies the left flank; these parts of the colon show the characteristic haustrations or sacculations of the large bowel. The sigmoid colon occupies the pelvis and does not as a rule show the same saccular appearance. Occasionally, there may be some difficulty in differentiating the sigmoid colon from the ileum, or the jejunum from the transverse colon, but the difficulty can usually be overcome by taking a further radiograph with the patient in a different position.

The radiographic technique is to take two films of the abdomen of the child, one an antero-posterior

projection with the child supine, the other a postero-anterior projection with the child either standing or suspended erect. The postero-anterior projection is used for the erect radiograph in order to produce less radiographic distortion of bowel shadows, and so to give a truer indication of the degree of distension.

As pointed out earlier, the physiological process is for the small bowel contents, both fluid and gaseous, to pass through the small bowel and on into the large bowel, a dynamic process. In the erect film, fluid levels indicate stasis at that site at the time that the exposure was made. The corresponding supine film will show in which parts of the bowel the gas is present, and if a mechanical block exists the most distal part of recognizable distended bowel will be in the region just proximal to the block. It should be remembered that in intussusception the obstruction is almost invariably at the proximal end of the process and so is in most cases a small-bowel obstruction.

Thus the radiological signs of mechanical obstruction in the small bowel are stasis in the small bowel, gaseous distension of the small bowel, and a complete absence of gas shadows from the large bowel. In some cases where obstruction is only partial, some gas bubbles may be present in collapsed bowel beyond the site of the obstruction. All gas shadows in the abdomen must be carefully studied; by identifying all the distended bowel, a relatively accurate localization of the site of the obstruction can be effected. By the same process a diagnosis of large-bowel obstruction can be established and localized. In a mixed series of over two hundred cases, adults and children, no case of large-bowel obstruction in a child was encountered other than those due to congenital anomalies such as an imperforate anus; in a previous paper the appearances of large-bowel obstructions in adults have been described (Middlemiss, 1948).

By this means obstruction can be demonstrated early, and elsewhere the author has published a case of intussusception in an infant diagnosed by straight radiography within twenty-four hours of the onset of symptoms (Middlemiss, 1948). The following cases have been selected to illustrate the points already mentioned.

Case 1. V.B., a girl aged 9 months, had a four-day history of vomiting and diarrhoea. During the last twenty-four hours the motions contained blood and mucus. On admission the baby was extremely ill and dehydrated. The abdomen was flabby and distended, but there was no palpable mass. Survey films (figs. 1 and 2) showed considerable distension of the small bowel (mostly the jejunum, but some ileum was recognizable), complete absence of gas shadows from the large bowel, and fluid levels present in the small bowel. This was regarded as evidence of a complete small-bowel obstruction in the mid or low small bowel. At operation an irreducible ileo-ileal intussusception was found; resection was performed, but the child died.

Case 2. K.A., a boy aged 5 months, had a cold and bronchitis fourteen days before admission. Thirty-six hours before admission he vomited and had obvious spasms of abdominal pain. Bowel action was normal at that time. The following day he started to vomit, passed blood in the motion, and was admitted to hospital. On examination he did not appear to be having much abdominal pain though he was obviously a poorly baby. There was no palpable tumour, and shortly after admission he passed a watery brown stool. He was thought to be suffering from gastro-enteritis. He took feeds for the next twelve hours without vomiting, and then passed another stool containing blood and started to vomit again. Survey films of the abdomen (figs. 3 and 4) showed very marked distention of a considerable length of small bowel, no gas in the large bowel, and, in the erect film, fluid levels in the small bowel. This was regarded as a complete intestinal obstruction occurring low in the small bowel. At operation an ileo-colic intussusception, the head of which had reached the hepatic flexure, was found and reduced. The patient made a good recovery.

Case 3. J.C., a boy aged 8 months, vomited intermittently for three days before admission. During this time he took some feeds but returned most of them. He had passed three stools a day, and for the last two days they had been hard but contained no blood. He had had no obvious attacks of abdominal pain. On admission he was an ill, dehydrated baby; the abdomen was a little distended, and it was considered that there was possibly a tumour in the right flank. It was not tender and nothing abnormal was detected per rectum. Survey films were taken, and the erect film (fig. 5) showed distension of the small bowel, mostly the ileum, containing fluid levels, and a complete absence of gas shadows from the large bowel; over the right ilium a single loop of ileum containing gas but collapsed and of normal lumen was demonstrated. It was considered that this was evidence of a partial low small-bowel obstruction. At operation the lower part of the ileum was found bound down to the posterior abdominal wall and obstructed by two enlarged lymph glands, and small tubercles were studded throughout the mesentery and generally throughout the abdomen. The obstruction was relieved, and the child recovered from the operation. When seen four months later the child was taking feeds normally.

Case 4. G.S., a boy aged 14 months, had been a healthy infant until three days before admission, when he was noticed to be pale and unhappy. He refused all food at that time and vomited, and subsequently continued to vomit frequently. He was completely constipated during the three days.

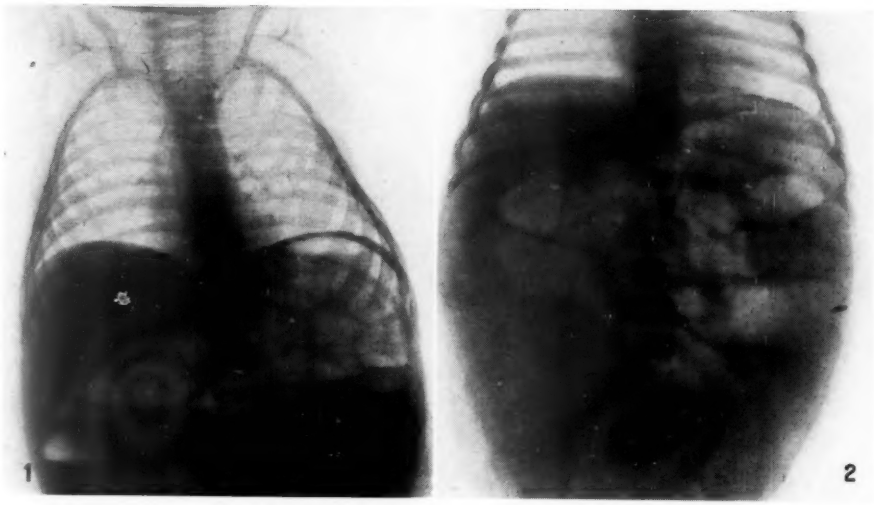

FIG. 1.—Case 1: erect film showing distension and fluid levels in small bowel.

FIG. 2.—Case 1: showing distended bowel to be mainly jejunum with some ileum and confirming complete absence of gas from large bowel (supine film).

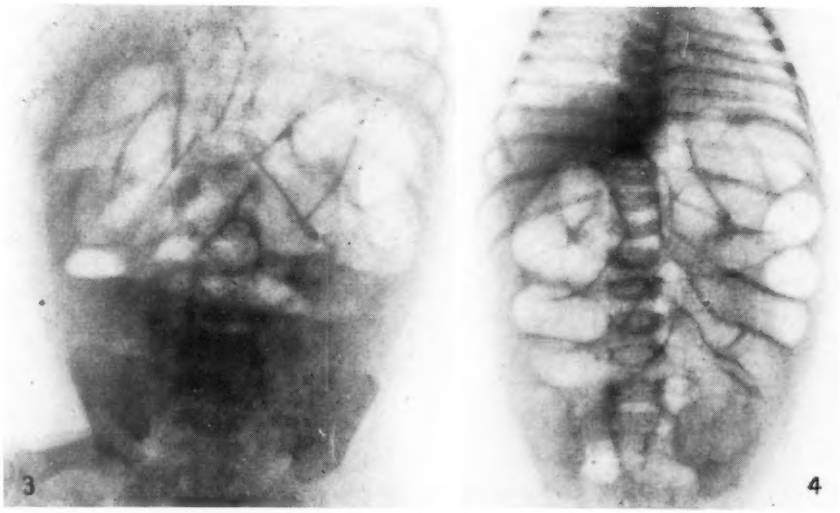

FIG. 3.—Case 2: erect film showing many distended loops of small bowel containing fluid levels.

FIG. 4.—Case 2: supine film showing that the distension involves a considerable length of small bowel, mainly ileum, and confirming complete absence of gas from large bowel.

PLATE I.

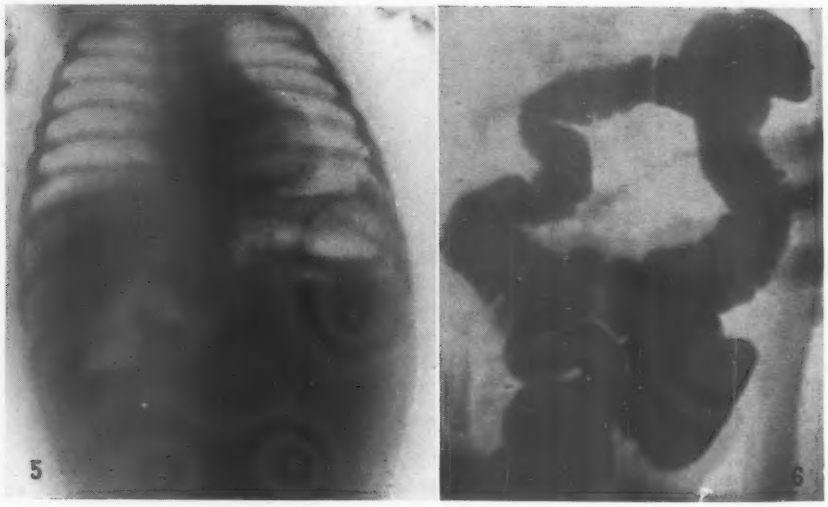

FIG. 5.—Case 3: erect film showing distension of loops of ileum containing fluid levels. There is no gas demonstrated in large bowel, but there is gas in a loop of ileum of normal lumen over the right ilium.

FIG. 6.—Case 4: taken during barium enema showing complete filling of large bowel.

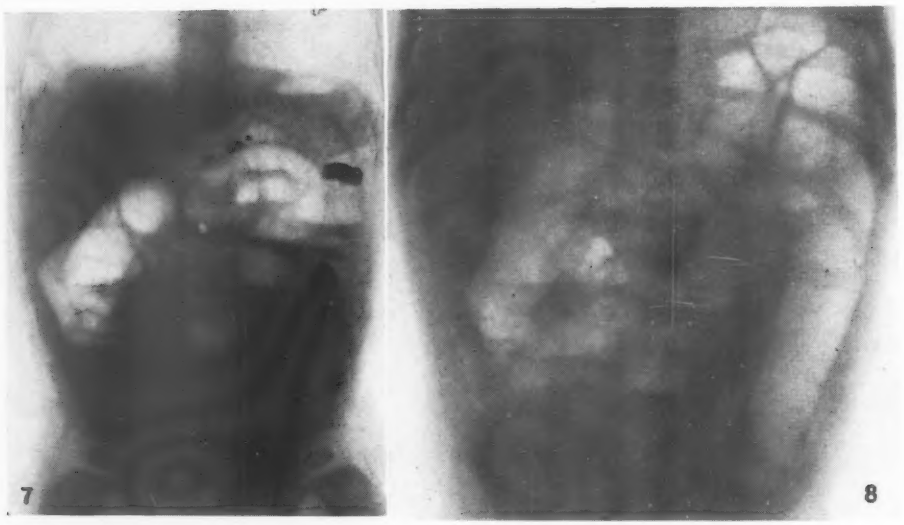

FIG. 7.—Case 4: erect film showing distension of loops of jejunum and ileum containing fluid levels, and complete absence of gas shadows from large bowel. Traces of barium remaining from the barium enema administered some hours earlier can be seen.

FIG. 8.—Case 5: erect film showing fluid levels in small bowel but in addition marked distension of large bowel.

PLATE II.

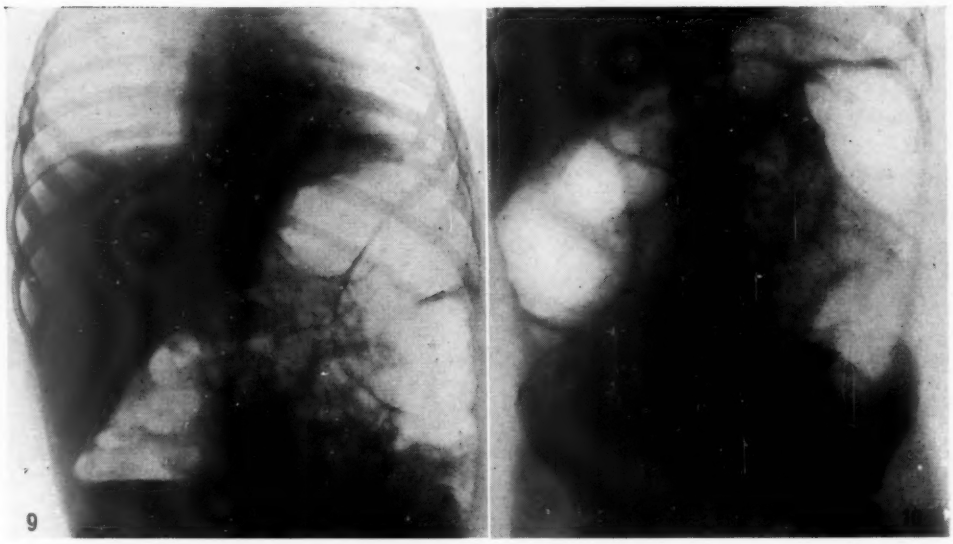

FIG. 9.—Case 6: erect film showing marked distension of many loops of bowel, some of them containing fluid levels. The length of bowel running along the left flank is shown not to have a fluid level at its lower end.

FIG. 10.—Case 6: supine film. Comparison with the erect film shows the fluid levels to be in small bowel and the ascending colon. Gaseous distension, however, extends as far as the distal end of the descending colon.

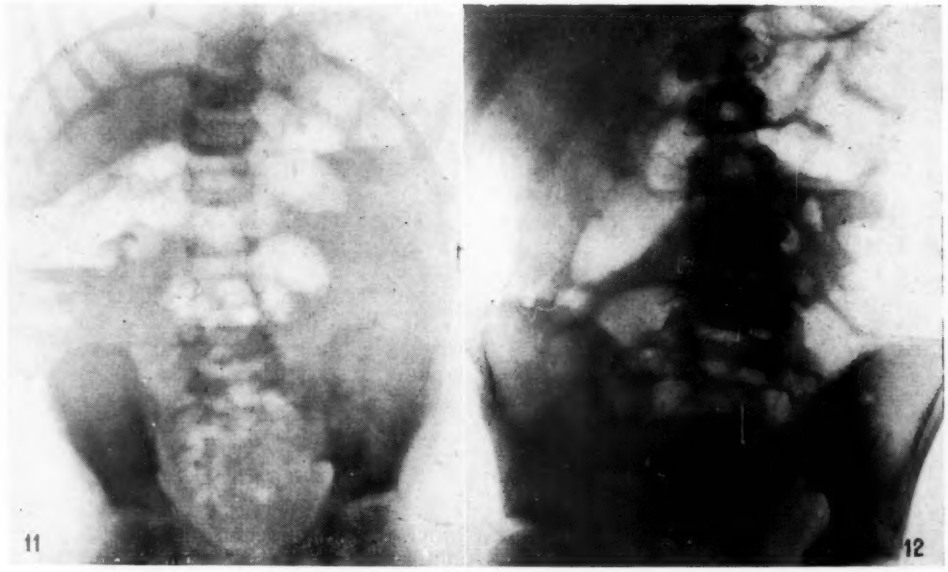

FIG. 11.—Case 7: erect film of a case of coeliac disease showing fluid levels in small and large bowel.

FIG. 12.—Case 8: supine film of an eight-year-old boy seven days after appendicectomy, showing distended loops of small and large bowel scattered throughout the abdomen.

PLATE III.

On admission to hospital he was a miserable, ill baby and appeared to be in pain. An enema removed a quantity of hard faeces from the rectum; there was no occult blood in the excreta. Intussusception being suspected, a barium enema investigation was carried out under screen control, but the large bowel was seen to fill completely (fig. 6). The infant returned to the ward, appeared to be improved, and took a feed; however, some hours later, as his condition again appeared to be deteriorating and vomiting had recommenced, a survey film of the abdomen was taken (fig. 7). This showed distended loops of small bowel, jejunum, and ileum, with evidence of stasis of bowel contents and no evidence of any gas in the large bowel; thus there was conclusive evidence of a low small-bowel obstruction, probably complete. At operation a loop of ileum was found bound down to a Meckel's diverticulum by an adhesion, and the bowel immediately proximal to this was twisted about the adhesion. The obstruction was complete. The adhesion was severed, the obstruction relieved, and the child made a good recovery.

It is obvious that the survey would have been carried out more profitably as a preliminary investigation.

Differential Diagnosis

The demonstration of fluid levels in bowel is not an indication of intestinal obstruction; that is a point which cannot be too strongly emphasized. Fluid levels merely indicate that at the time of exposure the contents in that part of the bowel in which the fluid levels exist are static. It is essential to analyse all gas shadows, to determine the site and distribution of the fluid levels, to assess the degree of distension of the bowel, and to establish the fact that gas does not exist in any quantity in the bowel beyond that part in which the fluid levels are present. In other words the state of affairs must be seen as a whole, and one isolated sign must not be fastened on and misinterpreted.

Case 5. Fig. 8 is the erect film of a boy of 6 months who presented with a history of three days' diarrhoea with green offensive motions, and obvious spasms of abdominal pain; ten hours before admission he passed dark red blood per rectum and began to vomit. After admission no stool was passed but vomiting continued. The baby was pale and dehydrated. No abdominal tumour was palpable, but he was considered possibly to have intussusception. The film showed fluid levels in the small bowel with some distension of the small bowel; but, in addition there was very considerable gaseous distension of the large bowel, in which no fluid levels could be detected. With such distension of the large bowel there obviously could not be a small-bowel obstruction. In fact after administration of sulphamezathine the child recovered rapidly from what had been a severe gastro-intestinal upset of an indeterminate nature. It should be noted that in the earlier stages the radiological investigation, though presenting certain features which might have been misinterpreted to indicate an obstructive lesion, in fact provided evidence to the contrary.

Case 6. Figs. 9 and 10 are the erect and supine films respectively, of a boy aged 4 years. He was admitted to hospital as a case of intestinal obstruction, acute abdominal pain having started about midday the same day. He was a flushed child, crying continuously, retching occasionally, but not actually vomiting. There was generalized abdominal distension with resistance on palpation but no obvious rigidity or tenderness. There were marked borborygmi. The x-ray investigation was carried out at 3.0 a.m., and the clinicians did not call in the radiologist on duty. On their own interpretation of the films, backed by the clinical signs and symptoms, they decided that the child was obstructed and they carried out an exploratory laparotomy. No obstruction was found. The films show distension of the small bowel and of the large bowel as far as the sigmoid colon; there are fluid levels in the small bowel and in the right half of the large bowel. This shows quite clearly that there is some intestinal disorder, but it equally clearly rules out the possibility of obstruction. The child subsequently developed left-sided pneumonia with effusion, and made a normal recovery.

This case shows the value of x-ray investigation in such disorders, and also the necessity for having a radiological opinion.

Case 7. Fig. 11 is the erect film of a child aged 4 years who had coeliac disease. A routine barium follow-through investigation was carried out, and scout films of the abdomen were taken beforehand. Clinically there is little likelihood of a case of coeliac disease being investigated for potential intestinal obstruction. It is of interest, however, to demonstrate the existence of fluid levels in such a case: the author has consistently shown this in such cases. Analysis of the gas shadows in the supine film of this case showed that the distribution was such that it could not under any circumstances be due to a mechanical obstruction.

These three cases serve to show that fluid levels may occur in bowel under many other conditions than those produced by mechanical obstruction. There is, however, one important class of cases in which they may occur and which it is important to differentiate from mechanical obstructions, that is, postoperative distensions. A postoperative distension may be traumatic, that is, a result of the handling of bowel during a laparotomy, or infective, for example, due to peritonitis. In most cases the process is a temporary or transitory one lasting from a few hours to three or four days. It may resolve, or it may become generalized, the so-called

'paralytic ileus.' Whatever the stage of the condition, it is primarily the inhibitory result of active stimulation of the sympathetic nerve supply to bowel-wall muscle. The radiological appearances show either a segmental or a general distribution; if segmental, the small and large bowel in one particular region in the abdomen are involved; if general, then the small and large bowel throughout the whole abdomen are involved. This involvement shows a distension of bowel by gas; the distension may vary from the size of the normal lumen of bowel to a very marked dilatation. In an erect film of the condition there may be fluid levels, and if so they are scattered throughout both the small and large bowel, showing no tendency to be restricted to the proximal end of the alimentary canal, as they are in mechanical obstruction.

Case 8. Fig. 12 is the supine film of such a case of inhibition ileus of infective origin. It is of a boy aged 8 years on whom seven days previously appendicectomy with drainage had been performed; peritonitis had ensued, with considerable abdominal distension. Subsequently a pelvic abscess was drained. The film shows generalized distension of the small and large bowel with some 'layering' between the loops of bowel, probably due to the peritoneal effusion. The erect film (unsuitable for reproduction) showed fluid levels with a similar distribution. The distribution of the gas shadows excludes the possibility of a mechanical obstruction.

It is of the utmost importance in such cases of postoperative distension to be able to differentiate between an inhibition ileus and a mechanical obstruction. In the event of a mechanical obstruction (due, for example, to adhesions) developing as a postoperative complication, its early diagnosis and differentiation from a simple postoperative distension may save life. This radiological investigation, while not necessarily infallible, is often a means of demonstrating earlier than by clinical observation the fact that a mechanical obstruction is developing or has developed. It is recommended that survey films of the abdomen be taken in all cases of abdominal distension persisting or developing after the fifth postoperative day. In doubtful cases this investigation should be repeated at intervals of twenty-four hours.

Summary

1. The appearances of mechanical obstruction of the bowel are: (a) stasis, as shown by the presence of fluid levels; (b) distension of bowel by gas; and (c) absence of gas shadows, or the demonstration of collapsed bowel distal to the obstruction. The site of the obstruction can be localized just distal to the most distal part of distended bowel.

2. Fluid levels may occur in bowel due to other conditions. Of these the most important is inhibition ileus occurring as a postoperative complication. In this, the small and large bowel are involved, either in one segment of the abdomen or throughout the whole abdomen, and the distension and fluid levels are not restricted to the proximal side of a block as in mechanical obstruction, but are distributed through the whole alimentary canal.

3. In a paediatric department, or indeed in any hospital, the contributions which this technical procedure has to make as an aid to clinical diagnosis may be listed as follows:

(a) it is essentially a time-saving factor, often enabling the establishment of earlier diagnosis and so providing for earlier surgical treatment before acute obstruction develops;

(b) it may provide a diagnosis in many cases in which the history and clinical signs and observation have failed to do so; this applies particularly to infants, and in many instances it may be the means of establishing a diagnosis when the alternative may be the spending of a further valuable twenty-four hours in clinical observation, which in turn may only lead to a delayed exploratory laparotomy;

(c) it is especially helpful in the observation of postoperative distension, particularly after the fifth day, when the clinician is on the look-out for the possible development of mechanical obstruction as a postoperative complication.

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PNEUMONIA IN THE NEWBORN RESULTING FROM THE INHALATION OF GASTRIC CONTENTS

BY

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In the course of performing post-mortem examinations in cases of neonatal death, we have noted the occurrence of pneumonia with certain special features, which we believe to be caused by the aspiration of stomach contents.

An extensive survey of the available literature published since 1920 revealed that little attention has been devoted to this condition. It was briefly described by one of us (Macgregor, 1939), and various other authors have recognized its occurrence, but an adequate description of the pathological features of the disease in infants or children was not discovered. The condition in adults has been described fully by Irons and Apfelbach (1940), and by Apfelbach and Christianson (1937).

A review of autopsy material at the Simpson Memorial Maternity Pavilion was undertaken, and it was discovered that this type of pneumonia is by no means infrequent.

The following is a review of the pathological features of forty-one cases that occurred during the period 1939-46 inclusive, with an analysis of the clinical and autopsy data.

Morbid Anatomy

Macroscopical features. The trachea and main bronchi showed intense congestion of the mucous membrane and mucopurulent exudate in the lumen. Foreign material was recognized only in early cases. In those of longer standing the material was obscured by inflammatory exudate or had been aspirated into the intrapulmonary bronchi.

The lungs showed widespread consolidation, which was most extensive and advanced in the bases and posterior borders. Areas of haemorrhage, sometimes very extensive, were invariably present. The cut surface was dark red, moist and friable, and oozed blood. Beads of pus, and sometimes recognizable vomitus, exuded from the cut ends of the intrapulmonary bronchi. Small areas of suppuration were occasionally visible, but these were more frequently found on microscopical examination. Post-mortem digestion of tissue was sometimes evident. Vesicular and interstitial emphysema were rarely observed. Pleurisy was unusual, except in the presence of underlying suppuration. When present, the pleural exudate was scanty and localized to small areas, frequently at the base. It could be wiped off without difficulty and the underlying surface looked normal. Gross empyema was found only when a lung abscess had ruptured through the pleura.

In many cases, although the macroscopical characters suggested the presence of this type of pneumonia, they were not sufficiently distinctive to permit of positive diagnosis without microscopical examination.

Microscopical features. The foreign material in the bronchi was heavily infected with bacteria, and the bronchial walls showed a severe inflammatory reaction (Plate IVa and b). Their surface was usually denuded of epithelium. The wall was severely congested and densely infiltrated with polymorph leucocytes. Purulent exudate was present in the lumen. Aspirated material in the alveoli excited a similar intense inflammatory reaction. This was invariably accompanied by massive haemorrhage, which was responsible for a large part of the consolidation and caused it to be confluent over wide areas.

Under low magnification, the architecture of the lung tissue in the vicinity of deposits of aspirated material was difficult to define because of digestion of the bronchial and alveolar walls and of their content of polymorph leucocytes and red blood corpuscles. The collagen and muscle fibres of the bronchial walls stained feebly with eosin, and the walls of the affected alveoli were also feebly stained. The nuclei of cells in the bronchial and alveolar walls, and in the inflammatory exudate, were pyknotic or had disappeared. A most striking feature was lysis of the red blood corpuscles in the exudate (Plate IVc). These had lost their haemoglobin, and the envelope of the corpuscles stained feebly with eosin, presenting a striking contrast with the unaffected cells in surrounding parts (Plate IVd). If sufficient time had elapsed between death and autopsy, the blood in the alveolar and bronchial capillaries also showed lysis. The changes resulting from digestion and lysis were related to the masses of aspirated material, and were less widespread than the inflammatory exudate or haemorrhage.

In the most advanced cases, foci of suppuration, which were sometimes confluent, developed in and around bronchi, causing complete disorganization of the bronchial wall and related alveoli. In such cases the development of a septic lymphangitis caused the spread of suppuration along the interlobular septa and by the peribronchial and perivascular lymphatic paths.

In certain cases, routine sections of pneumonic lungs showed the features of an established neonatal bronchopneumonia, with, in addition, small areas of recent aspiration pneumonia. It was usually easy to determine the secondary or terminal nature of these foci resulting from aspiration.

Bacteriology

Unfortunately, owing to technical difficulties caused by the 1939-45 war, bacteriological investigations could be undertaken in only a few cases. In nearly all the cases that were examined, cultures of Bacillus coli were obtained, frequently in association with indifferent streptococci, and occasionally with Monilia albicans. In a number the results were rejected because control smears of the lung juice failed to indicate satisfactorily that the organisms obtained in cultures were present during life (Macgregor, 1939).

Types of Pneumonia Excluded from this Study

We have not included in this study cases in which material from the stomach had been aspirated into the respiratory passages shortly before death and had produced no gross or microscopical evidence of any effect on the lungs.

We have also excluded cases of staphylococcal pneumonia, in which suppuration frequently occurs and is usually more extensive and of more rapid development than in the cases under consideration. Although haemorrhage and necrosis are typical features, digestion of tissue does not occur, and lysis of blood is only occasionally seen. Staphylococcus aureus is usually the only organism present, and it is therefore unlikely that this type of pneumonia is the result of aspiration of stomach contents, which contain a variety of bacteria. It is more likely to be caused by aspiration from the mouth or pharynx of food or secretion heavily infected with staphylococci.

Cases of aspiration pneumonia caused by congenital atresia of the oesophagus with tracheo-oesophageal fistula have also been excluded.

Incidence

During the years 1939-46 inclusive, 962 autopsies were performed on infants born alive who died in the Simpson Memorial Maternity Pavilion, Royal Infirmary, Edinburgh. Of these, 939 died within one month of birth. Among these there were forty-one cases of pneumonia resulting from the aspiration of gastric contents. Thirty-nine of the infants were less than one month old. In thirty-six cases the pneumonia was believed to be caused entirely by aspiration. In the remaining five it was thought that pneumonia had existed before aspiration occurred, because the lungs showed established bronchopneumonia, complicated by small areas of recent aspiration pneumonia.

A remarkable increase in the incidence of aspiration pneumonia was observed during the last two years of the period. During the six years 1939-44, when 731 autopsies on infants born alive were performed, fourteen cases occurred (1·9 per cent.). During the two years 1945-46, when 252 autopsies were performed, twenty-seven cases occurred (10·7 per cent.).

Clinical Features

We have found no evidence that this type of pneumonia differs in its clinical characters from other types which occur during the neonatal period, and diagnosis can only be established with certainty by pathological examination. In only one of the forty-one cases was a definite diagnosis made because the occurrence of aspiration was observed, and was followed by the development of severe and rapidly fatal bronchopneumonia.

Incidence in Relation to Birth Weight

In fig. 1, incidence is plotted in relation to birth weight, the ordinate indicating the number of cases, and the abscissa the birth weight. The standard of prematurity applied was the accepted one: infants of 5½ lb. and under at birth were regarded as premature. A vertical line drawn at 5½ lb. separates the mature on the right from the premature on the left. Thirty-three of the infants were premature, and of these twenty-four were under 4 lb. in weight.

Incidence in Relation to Age at Death

In fig. 2 the ordinate represents the number of cases and the abscissa the age at death in days. Twenty-five of the infants died between the fourth and ninth day.

Maternal Health during Pregnancy

In twenty-six of the cases pregnancy had been normal; in seven the mother suffered from pre-eclamptic toxaemia, in one from hypertension, in another from chronic cardiac disease, and in one the mother's blood Wassermann reaction had been positive. Five infants were admitted to hospital after birth, and no details of the maternal history were available.

Type of Delivery

Delivery was spontaneous, either vertex or breech, in twenty-five cases. Four breech extractions required assistance. Ten infants required forceps delivery, and two deliveries were by Caesarian section.

Condition of the Infant at Birth

An attempt to correlate the condition of the infants at birth with the occurrence of aspiration of stomach contents proved difficult. Because of shortage of staff caused by the war, the recorded information was inadequate in most instances, and the cases in which information was available were too few to allow any conclusions to be drawn from them. It was noteworthy that most of the infants who died during the first four days were in an unsatisfactory condition at birth.

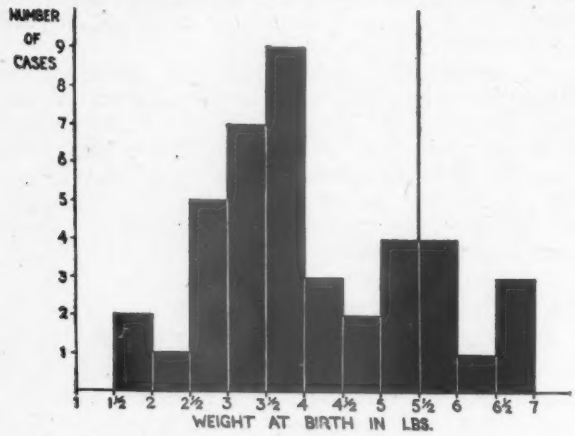


FIG. 1. Incidence in relation to birth weight, 41 cases.

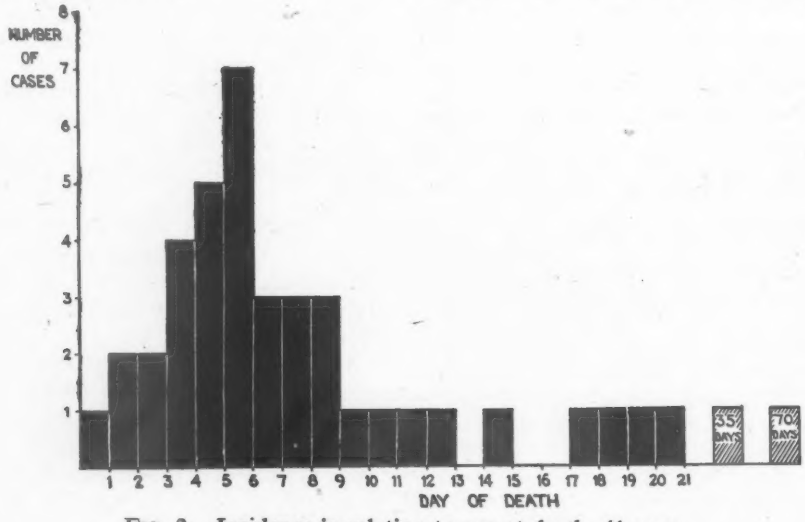


FIG. 2.—Incidence in relation to age at death, 41 cases.

Associated Conditions in the Infant

Three infants had developmental abnormalities: one was a mongol, another suffered from hydrocephalus with meningocele, and the third infant had atresia of the duodenum.

Eighteen infants suffered from intracranial haemorrhage, and in nine of these the condition was severe.

Five infants suffered from thrush infection: in two it was confined to the oral cavity; in three the oesophagus was also involved. In one case there was peptic ulceration of the lower end of the oesophagus.

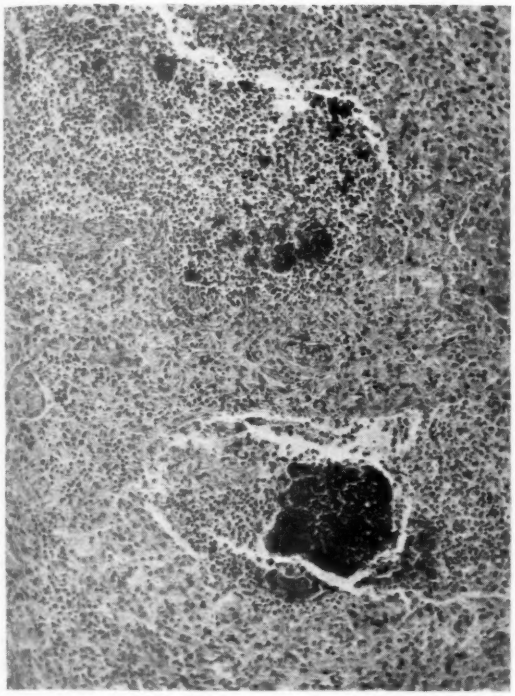
Ten infants were known to have vomited. In one case the vomiting occurred more than two weeks before death and was probably not responsible for the pulmonary condition, but in the other nine the vomiting may have been of importance in the etiology of the pneumonia.

Type of Feeding

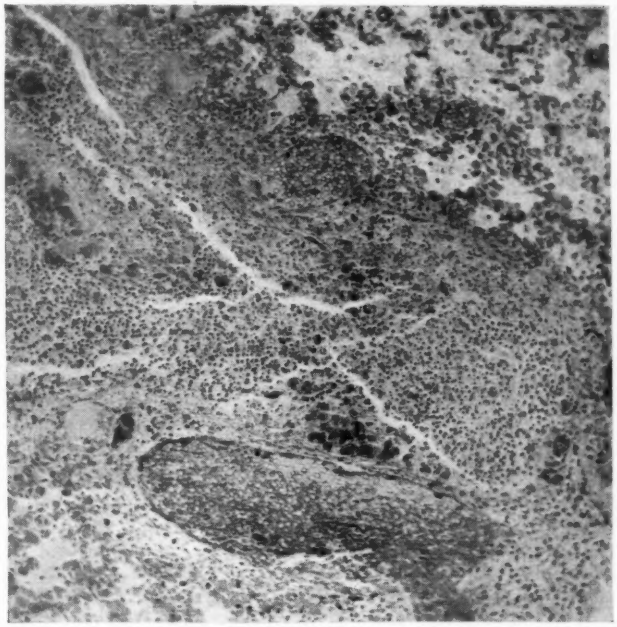
Only six infants were entirely breast-fed; fourteen received expressed breast milk only; eight received breast milk and complementary feeds, and eleven infants received artificial feeds. Three of the infants were fed by oesophageal tube. In two cases no details of the method of feeding were available.

Discussion

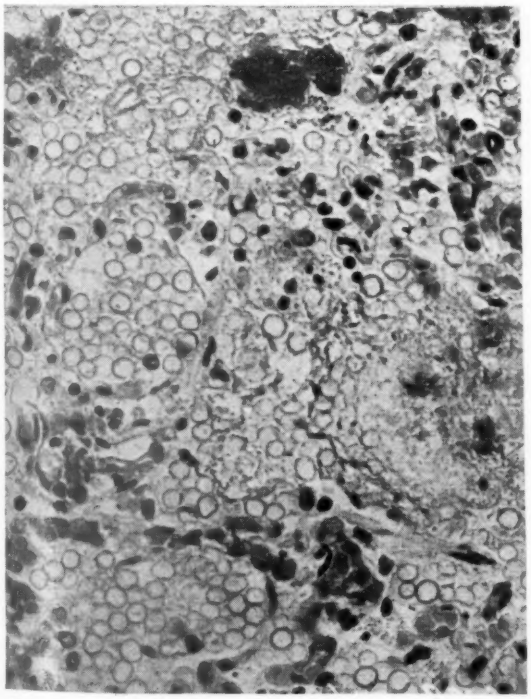
The description of ' aspiration pneumonia ' by Irons and Apfelbach (1940) corresponds closely to the condition we have described in the newborn. These authors call attention to the characteristic features of the microscopical picture, noting that ' the tissues removed from the thorax have lost their capacity for distinct staining in contrast to tissues removed from other portions of the body, indicating a disproportionate degree of post-mortem change in the lungs. The erythrocytes in the alveolar spaces, and often those in the capillaries, have lost a large amount of their hemoglobin so that they stain only as shadowy outlines.' They emphasize the importance of this, ' because in instances of pneumonia caused by the usual respiratory organisms hemolysis and post-mortem change are not characteristic of the alterations in lung tissue.



(a).—Bronchi containing masses of aspirated material and showing acute inflammation which obscures their walls. Haematoxylin and eosin. × 100.



(b).—A bronchus which contains aspirated material and shows incipient suppuration. An adjacent vein shows post-mortem lysis of erythrocytes on the side nearer the bronchus. Haematoxylin and eosin. × 100.



(c).—Lysed red blood corpuscles in alveoli; the lysis is in relation to deposits of aspirated material. Haematoxylin and eosin. × 400.

(d).—Illustrates an area of haemorrhage and pneumonia in part of which lysis and digestion have occurred. Haematoxylin and eosin. × 100.

PLATE IV.

. . . Thus, advanced changes in the lungs indicate that material has been introduced into them that can accelerate post-mortem alterations.' In the opinion of Irons and Apfelbach digestion of tissues and lysis of blood occur only after death. They stressed the importance of performing autopsies within an hour or two of death, because the post-mortem changes produced by the aspirated material are then more readily recognized than when generalized post-mortem changes have occurred. In most of our cases it was not possible to perform the autopsy so promptly, and on histological examination the blood in the alveolar capillaries had usually undergone lysis. This had obviously occurred after death, but as an aid to diagnosis it was nevertheless significant, as it occurred only in areas related to aspirated gastric contents.

Irons and Apfelbach introduced stomach contents, in which there was no free hydrochloric acid, into the bronchial tree of a dog and produced ' the same types of haemorrhagic, hyperaemic and oedematous alterations in the lung . . . as are observed in persons in whom the pathologic changes interpreted as aspiration bronchopneumonia are found at necropsy.'

Apfelbach and Christianson (1937) found that the introduction into the lungs of animals of ' gastric fluid containing normal amounts of hydrochloric acid usually did not produce death, but a temporary hyperemia of the lungs occurred. Also stomach content free of hydrochloric acid and containing bacteria, when passed through a Berkefeld filter, also produced only a transitory hyperemia of the lungs. Death occurred in animals only if stomach content containing bacteria was used.' (Irons and Apfelbach, 1940).

Miller (1941) showed that the gastric acidity of normal full-time infants is usually high at birth but falls during the first ten days of life and thereafter gradually rises. In premature infants the gastric acidity is much lower during this period. In view of these observations it seems possible that hyperaemia induced by the inhalation of gastric contents containing free hydrochloric acid might be a factor in the production of the massive pulmonary haemorrhage that was observed in many of these infants. This haemorrhage sometimes caused death before the development of much inflammatory reaction. In the absence of free hydrochloric acid, effects would depend to a greater extent on bacterial growth and would therefore be slower to develop (Simonds, 1940).

Frank vomiting to which aspiration could be attributed was recorded in a minority of cases. We believe that regurgitation, to which less attention may be paid, is also of great importance. It may occur without being noticed by the attendants, and, unless regurgitated material escapes from the mouth and stains the infants' clothes, there may be nothing to indicate that it has occurred. There is a great risk that regurgitation may occur during feeding unless adequate care is being taken.

Aspiration of material from the mouth will be favoured by insensitivity of the protective reflexes of the pharynx and respiratory tract. Prematurity, feebleness, deep sleep and narcosis, intracranial haemorrhage, and chilling are some of the factors that are known to depress the activity of these reflexes (Amberson, 1937; Nungester and Klepser, 1938). Prematurity is often associated with several other of these factors, and this probably explains the high incidence of aspiration pneumonia in premature infants. In our series several infants died of aspiration pneumonia within four days of birth. We believe that there is a grave risk of aspiration of gastric contents when infants are fed while still suffering from the effects of birth stress or maternal narcosis.

We have called attention to the striking increase in the incidence of aspiration pneumonia during the last two years of the period under survey. It would be unwise to draw dogmatic conclusions from this observation, but during these two years the work of the hospital greatly increased without a corresponding increase in the nursing staff. Under such circumstances the amount of time and care devoted to each infant would of necessity be reduced. Further observation at a later time will be required to show that improved conditions of staffing bring about a reduction in the incidence of aspiration pneumonia.

Summary

A review of forty-one cases of pneumonia resulting from the inhalation of gastric contents is presented.

The main pathological features are extensive consolidation with haemorrhage and a tendency to suppuration. Microscopically, digestion of tissues and lysis of blood in relation to aspirated material are characteristic.

An analysis of the clinical data is given.

Attention is drawn to predisposing factors with particular reference to prematurity.

An increase in the incidence during the last two years of the period under review was observed. It is suggested that this may be related to a shortage of nursing staff.

We wish to express our thanks to Professor Charles McNeil, Professor R. W. B. Ellis, and Dr. J. L. Henderson for helpful criticism and access to clinical records.

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JUVENILE THYROTOXICOSIS TREATED WITH THIOURACIL

BY

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(From the Royal Hospital for Sick Children, Edinburgh)

Prepubertal thyrotoxicosis is a condition of some rarity and comparatively few childhood cases have so far been recorded in the literature where the drug thiouracil has been used in treatment. A review of six cases so treated was published by Williams and Janney (1947). The present case provides a suitable example both of the clinical picture and the response to treatment.

Atkinson (1938) in a survey of world literature collected two hundred and eight cases of Graves's disease in children from the years 1851 to 1938. Of these, only 20 per cent. occurred in the age period six to nine years. The registers of the Royal Edinburgh Hospital for Sick Children record only two previous undoubted cases since 1925 of a total of over seventeen thousand children admitted to the medical and surgical wards.

Case Report

I.S. was admitted to the Royal Edinburgh Hospital for Sick Children on Feb. 3, 1948, aged 6¾ years. The illness dated from an attack of measles in the autumn of 1946, following which the child became emotional and jumpy with a tendency to drop things and to make restless, twitching movements with the hands. She was frequently off school with bouts of ' fever,' and her own doctor, to whom the case presented as one of chorea, insisted on rest in bed for three months.

In May, 1947, the mother first noted that the child's eyes were becoming more prominent, but she did not mention this when reporting with the girl to the out-patient department of the Royal Hospital for Sick Children in June of that year. Hospital admission was not practicable, and the diagnosis remained unchanged. She was sent home to bed with a recommendation for tonsillectomy, as the tonsils were enlarged and obviously infected. Phenobarbitone and aspirin were prescribed. An attempt was made to send her back to school at the close of the summer vacation, but she was ' always tired ' and had ' a hot skin.' She was found, once again, to be running a low-grade fever, and she was kept in bed for a few days at a time.

In November, 1947, a swelling at the root of the neck was noted, and the child was sent for by the local hospital for tonsillectomy, only to be returned home unfit for operation. The tonsils were acutely inflamed, the associated lymph glands were enlarged, and the right ear was discharging. During the month of January, 1948, the picture became even more typical with visible loss of flesh, insomnia, and excessive appetite.

The child's early development had been uneventful. As a baby she was breast-fed for fourteen days only. Her only previous illness had been whooping-cough at four years. The family stock was healthy, with the important exception of a maternal aunt of twenty-nine years who had a thyroidectomy for Graves's disease in October, 1947. The child spent much time in this aunt's company, and they had always been very fond of one another. The mother, although healthy, showed very slight diffuse thyroid enlargement. Conditions at home were comfortable, and there was no discord in the family, which was ' very happy at all times.' At school, the child was popular with teachers and scholars and, if anything was ' too interested in her lessons.' The child had not been subjected to corporal punishment, nor had she suffered from any other known physical or psychic shock. The two younger siblings were healthy.

On admission to hospital the child was tall (see fig. 1) for her age; she measured 51¼ inches, and weighed 51¼ lb. She was fair-haired, pale, slender, and keenly interested in her surroundings. She talked freely without shyness, laughed too readily, and was equally liable to burst into tears. She was in no way distressed. She remarked that she was always hungry and always hot, and that she sweated if made to wear a coat.

The bony skeleton showed no abnormality and the bone age radiologically was that of a white girl of 8¾ years. The skin was very warm, flushed, and moist, the handshake giving the characteristic sensation. Nutrition was poor, although the fatty layer was evenly distributed; the scapular and anterior iliac spines were prominent. Muscle tone and posture were rather poor.

A diffuse, readily visible fullness in the root of the neck presented the shape of the thyroid gland and moved on deglutition (fig. 3). The surface was finely granular, and a well-marked bruit was present on auscultation. The neck circumference one inch

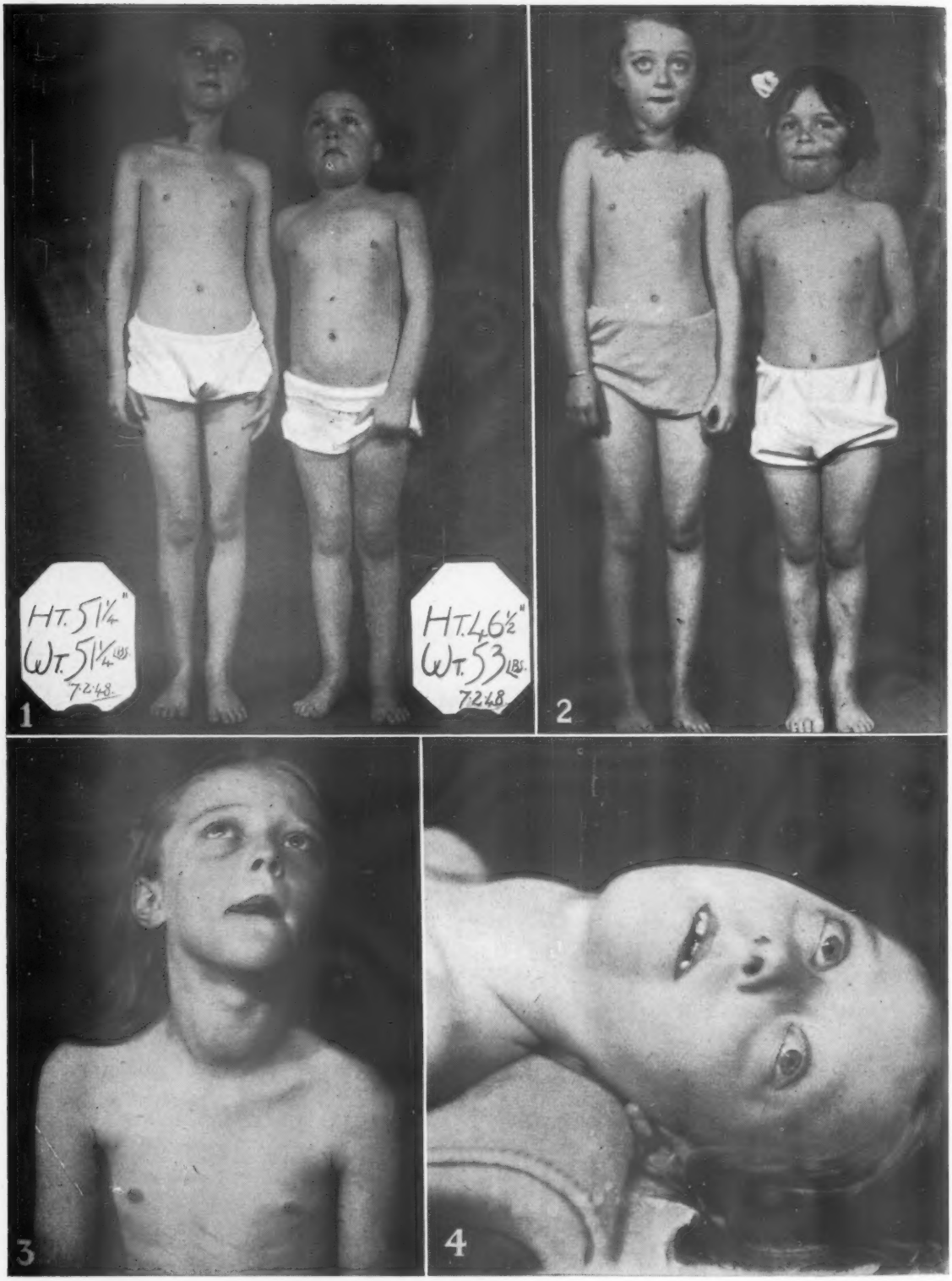

FIG. 1.—Before commencing treatment with thiouracil. Girl on the right is a healthy child of the same age.
FIG. 2.—After ten weeks of treatment in hospital.
FIG. 3.—On admission, showing the goitre.
FIG. 4.—On admission, showing the goitre and exophthalmos.

PLATE V.

above the sternal notch was 10·6 inches. The eyes were symmetrically prominent (fig. 4) and there was evidence of lid lag. The hands were in ceaseless motion while she spoke, but were not choreiform. Unlike a case of chorea, she could, with concentration, print her name very neatly in block capitals with a pencil on paper. A fine tremor of the outstretched fingers was present. The glucose tolerance curve was normal, and the urine free from sugar and ketone bodies. Although the clitoris appeared a little hypertrophied, there was no other evidence of precocious puberty. A qualitative test for follicle-stimulating hormone in the urine proved negative. Stereoscopic radiographs of the skull showed no pathological increase in the size and shape of the sella turcica. A persistent tachycardia at rest was present, and the pulse pressure was high on palpation. Clinically and radiologically the heart was not obviously enlarged; there was a very soft systolic murmur in the mitral area, the second sound being accentuated in the pulmonary, but not in the aortic, area. The blood pressure at rest was 126 systolic and 62 diastolic. The skin flushing has already been described. In the respiratory system the only abnormality found was the infected state of the tonsils, which were very large but had no associated adenitis. Straight radiographs of chest were negative, and also the Mantoux test (1 in 1,000). The ears were healthy. The tendon reflexes were brisk, those of the knee being sustained.

The blood picture on admission was: Haemoglobin 83 per cent.; red blood cells 5·55 million per c.mm of blood; colour index 0·76; white blood cells 13,800 per c.mm.; reticulocytes less than 1 per cent.; neutrophils 48·6 per cent.; eosinophils 2·2 per cent.; large lymphocytes 12·4 per cent.; small and intermediate lymphocytes 31·2 per cent.; monocytes 5·6 per cent. The red cells were fairly well filled, and there were many platelets present.

Progress. In order to facilitate the description of the response to treatment, this has been recorded graphically and only a few explanatory notes will be added to each diagram. Following the eleventh week of treatment, the recording of clinical data was much less frequent owing to the usual changes in the resident staff.

A control period of two weeks in bed with adequate phenobarbitone sedation resulted in no clinical improvement and, in view of the child's toxic state, it was decided to delay no further and thiouracil 100 mg. thrice daily was commenced.

General appearance. The appearance of the child eleven weeks after beginning treatment is shown in fig. 2. It not only shows the improved

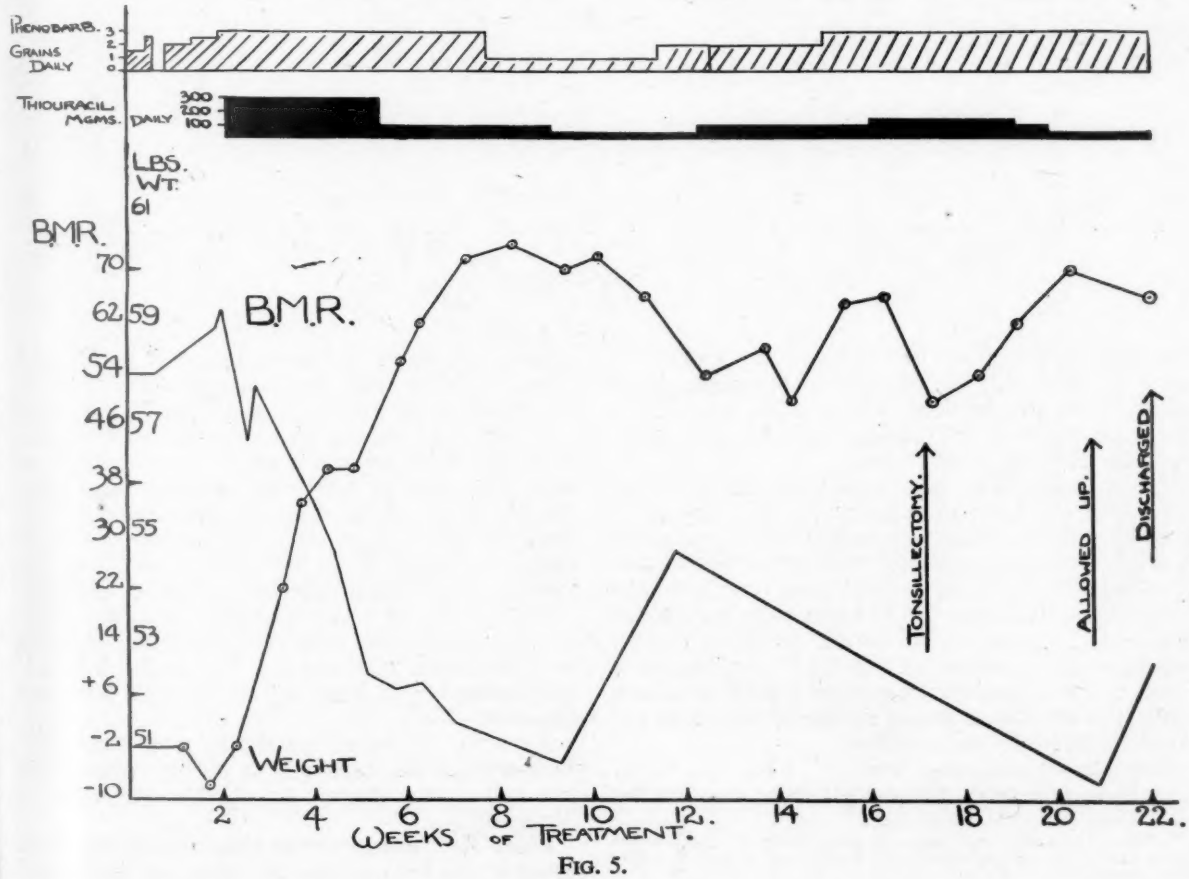

FIG. 5.

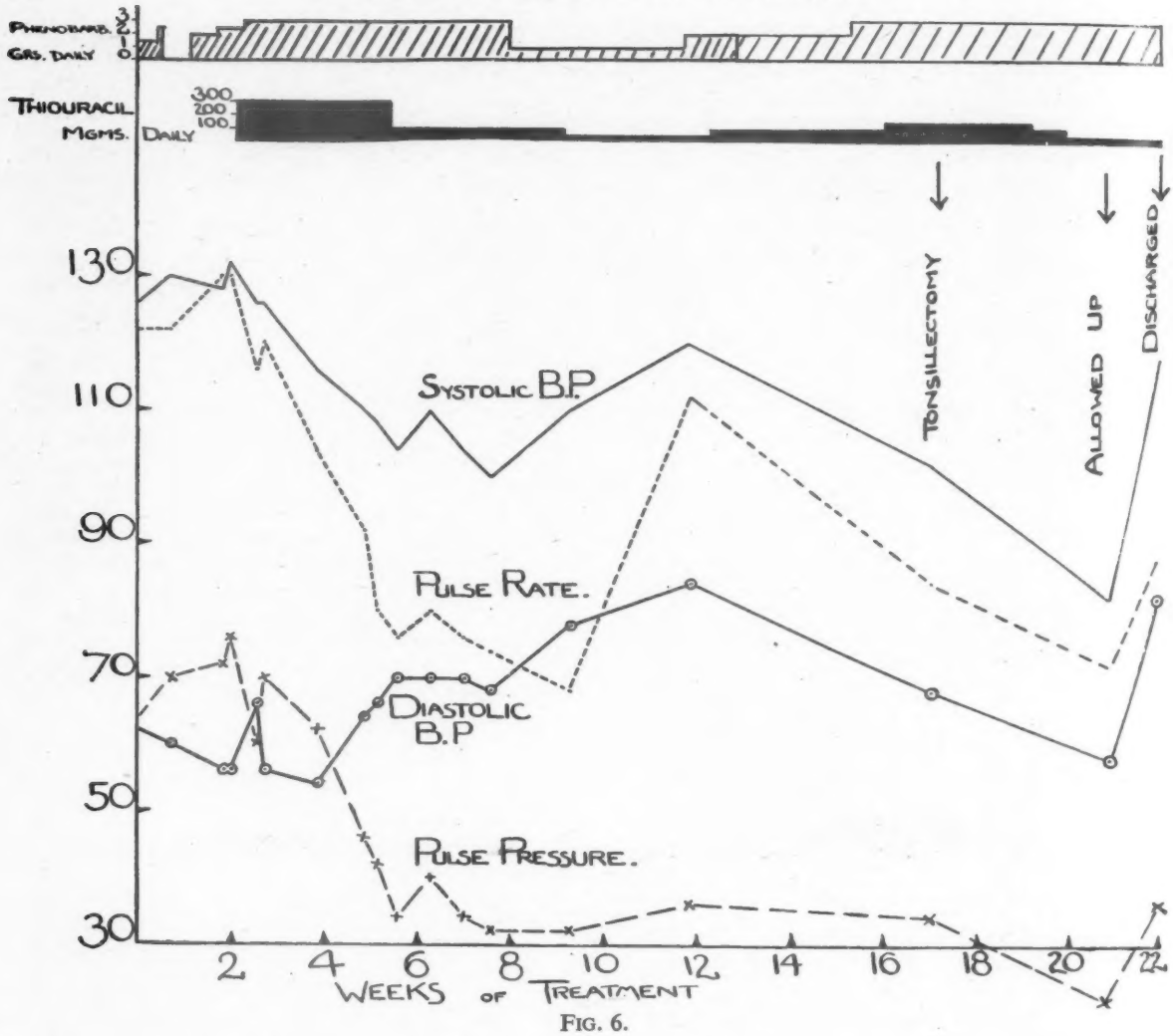

FIG. 6.

nutrition but it has also captured the emotional state of the child. In the first photograph she is tense, alert, and nervous, whilst in the second she is lax and plump; the change is almost reminiscent of 'The Taming of the Shrew.'

BASAL METABOLIC RATE (fig. 5). In a highly emotional child, the use of any apparatus involving breathing into a mask was excluded as a means of giving an accurate reading. Assessment by calculation from the insensible perspiration presented other possibilities of error, and it was finally decided to make use of the formula devised by Read (1922). Accurate measurement of the basal metabolic rate is not claimed, but it is felt that the results* obtained while the child was asleep at twelve midnight are comparable in the same subject.

Having attained the level of +62, the basal metabolic rate made a most dramatic response to thiouracil therapy, flattening out on attaining single figures. When the maintenance dose was cut further from 50 mg. twice a day to 50 mg. daily, however, the basal metabolic rate again rose steeply to +27·5 in the twelfth week of treatment and was only controlled by increasing the dose once again. Tonsillectomy at the beginning of the eighteenth week resulted in further improvement, but the figure increased to +10·5 when the child was allowed to run about the day before her discharge.

WEIGHT (fig. 5). This was the most striking index of progress and the rapid rise was dramatic on the commencement of thiouracil. A careful record of fluid balance was kept and at no time was there retention.

As with the basal metabolic rate, the weight flattened out on reduction to 50 mg. twice a day and fell quite steeply on further reduction to 50 mg. daily.

From the fourteenth to the seventeenth week, however, she became very excitable and restless and

* Read's formula states that the basal metabolic rate=0·683 (pulse rate+0·9×pulse pressure)—71·5 when the subject is under basal conditions.

the weight was erratic. It had been originally intended to delay tonsillectomy until her general condition improved, but in view of her continued illness and their infected state, the tonsils were now removed under the protection of systemic penicillin.

CARDIOVASCULAR CHANGES. Fig. 6 represents changes in the cardiovascular system and needs little explanation. Once again the findings seem to depend directly upon the dose of thiouracil given. The falling systolic and rising diastolic pressures with resultant fall in pulse pressure are instructive while the sudden increase in the sleeping pulse rate on lowering of the thiouracil dosage to 50 mg. daily is most significant.

The sudden rise in all readings on the eve of the child's discharge was a response to a day of unrestricted activity after eighteen months of rest and the fact that the basal metabolic rate, which depended directly upon them, remained at +10·5 is surely a tribute to therapy.

BIOCHEMICAL DATA

Blood cholesterol (fig. 7). The blood cholesterol has frequently provided scope for argument in the assessment of thyroid activity.

Its importance was stressed by Hurxthal (1933), while Gildea et al. (1939) thought that it more frequently rose above normal in myxoedema than it fell below in hyperthyroidism. Schmidt (1935) believed it could not be correlated with the basal metabolic or other objective measures of thyroid activity, and more recently Dunlop (1948) had abandoned its use in thyrotoxicosis under treatment. Certainly in this single case of juvenile thyrotoxicosis it has proved the least sensitive and the most useless of the measures employed.

Creatinuria (fig. 7). Kepler and Boothby (1931) among others studied the urinary excretion of creatine in hyperthyroidism, while Palmer et al. (1929) discussed the influence of iodine upon the creatinuria of thyrotoxicosis.

It was begun in this case solely out of interest and has shown itself to be simple and possibly sensitive. The total urine passed in twenty-four hours was noted and a sample from the collection was subjected to a comparatively simple but accurate analysis for (a) creatinine, and (b) creatinine + creatine. The creatine excretion, after a dramatic fall, rose again on the smaller dosage of thiouracil, but fell to near zero on 150 mg. thiouracil daily with tonsillectomy. The final reading was omitted as the child was up and about and part of the twenty-four hour collection was lost, thus invalidating the results as the excretion of creatine is irregular through the twenty-four hours.

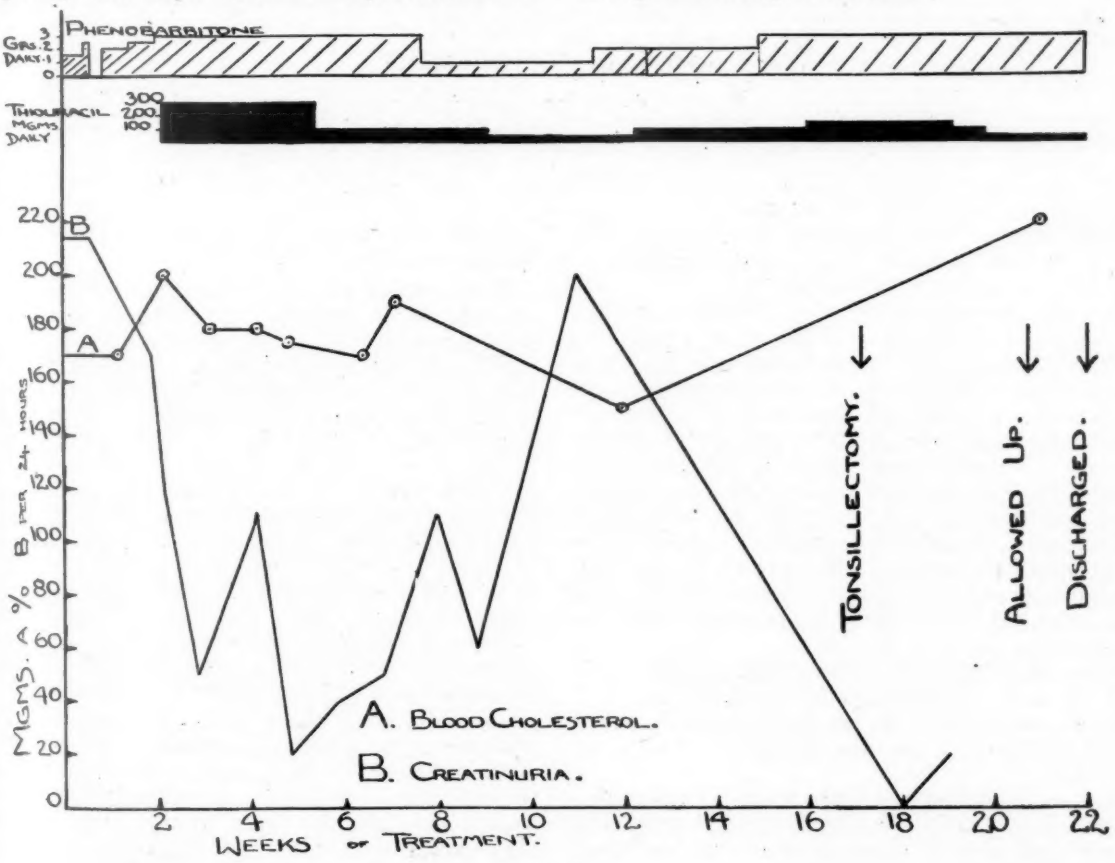

FIG. 7.

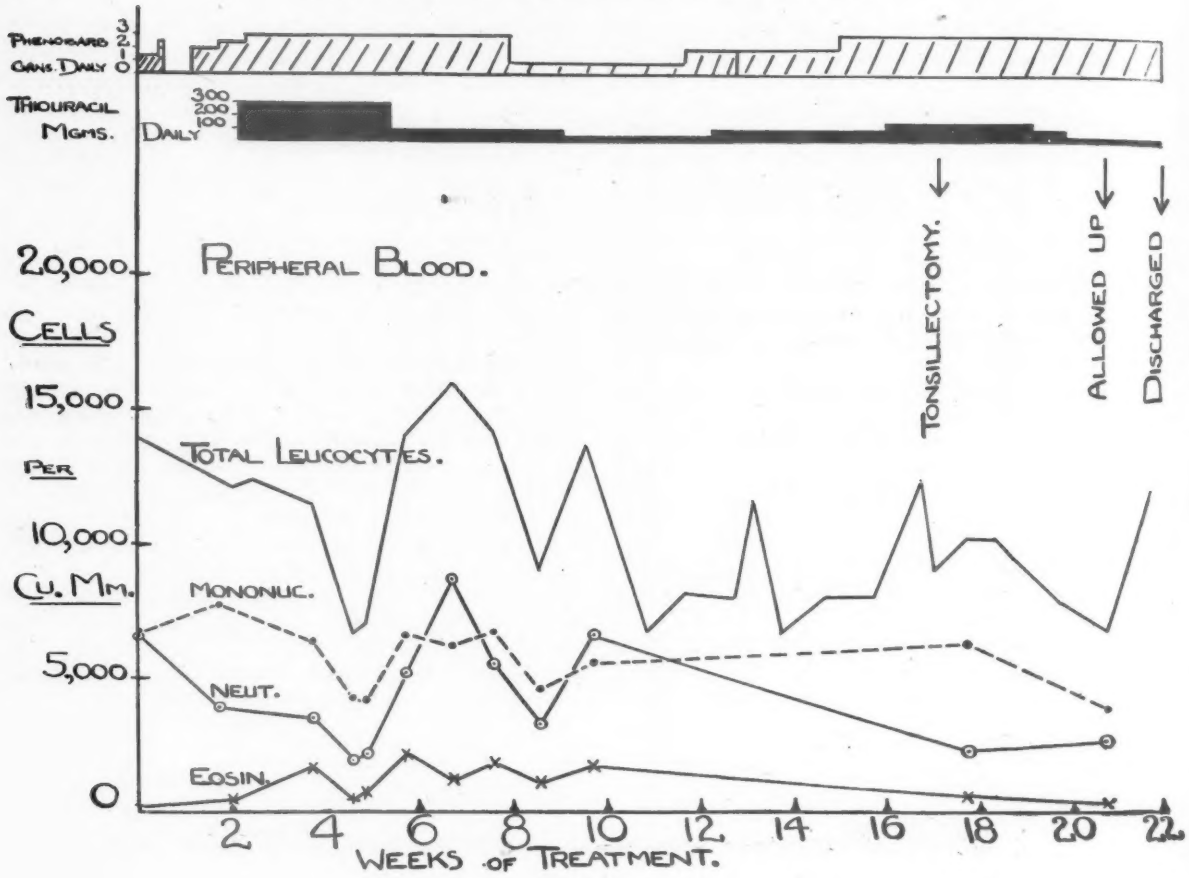

FIG. 8.

Calorimetry. The results of this investigation have not been included as it was not possible to maintain a constant environment.

An efficient calorimeter was produced and the child's hand immersed in a measured volume of water for a given time at room temperature. The temperature rise was noted and the energy liberated in gramme calories per minute was calculated. Insulation was achieved by plastic polythene sleeving. Readings were taken at the same hour after the lunch-time meal, and the ward temperature was kept as constant as possible. The graph showed an interesting, if fortuitous, parallel to the daily output of creatine. Owing to the temperature change from winter to summer during the course of treatment, it was reluctantly decided to abandon the investigation.

Blood picture (fig. 8). The general blood picture showed, as was expected, a fall in total neutrophil polymorphonuclear cells on the increased, and a return to normal on the decreased, dosage of thiouracil.

Williams and Janney (1947) noted an increase in the total eosinophil count, which reached a maximum at the sixth week of thiouracil treatment and then became reduced. In the present case a similar increase was noted, reaching a maximum in the fourth week of treatment.

The peaks of the total leucocyte count rose with almost regular periodicity and whilst there is no direct evidence that this relates to oestrogenic activity, it is a possibility which might be considered. Ingiulla (1947) has discussed the leucocyte response to the administration of oestrogens in the newly born.

OTHER FACTORS. Throughout her illness, the child was a behaviour problem in the ward, but it was felt that this was largely due to the fact that her health was improving and she found rest in bed more and more tedious as the months passed. Although she was very 'wild' on discharge, it was the state of a healthy, spirited girl, perhaps somewhat spoiled by over-attention, and was not the labile emotional instability of the early weeks.

Sleep did not behave as at first expected. On admission it was virtually impossible to arouse the child at night by any means short of physical violence, but on discharge, although sleep was sound, she could be made to stir, sedation being identical at both periods. Tolerance to phenobarbitone may have played a part. Concentration

on simple arithmetic or puzzles improved with treatment, but was never good.

Again contrary to expectation, the circumference of the neck remained almost contant throughout, with a variation never exceeding 0·5 inches. There was possibly some improvement in the exophthalmus, and lid lag was not present on discharge from hospital.

Progress after discharge from hospital. The child has been seen at two- to four-weekly intervals since her return home, the last attendance being on Sept. 22, 1948. Thiouracil therapy has been kept constant during this time, but owing to drowsiness the dose of phenobarbitone was reduced from 1 gr. three times daily to 1 gr. at night on Aug. 16, 1948. Her general improvement has been maintained, and is reflected in her nutrition, posture, and general behaviour. Since Aug. 30, 1948, she has been attending school regularly without disability. Her weight on Sept. 22, 1948, was 62·5 lb., a considerable gain since discharge. The skin was cool and dry and there was less pronounced exophthalmos, but the neck circumference had increased to 11⅛ inches. The systolic blood pressure was 98 mm. and the diastolic 68 mm., with a pulse pressure of 30 mm. The heart rate was 76 and regular, although the child was awake and had just completed a long journey to Edinburgh, in contrast to readings in hospital which were taken during sleep. Using Read's formula as before, a value of −1·2 was obtained. Throughout the period of observation as an out-patient, total leucocyte and differential counts were made, the only significant change being an eosinophilia of 11 per cent. on Aug. 30, 1948. This subsequently fell to 7 per cent on Sept. 22, 1948.

Discussion

It is not possible to draw conclusions from a single case, but should this observation be substantiated by other similar cases it would seem that in thiouracil and its derivations we might have an answer to Beilby and McClintock's (1937) statement that 'it is far more dangerous to attempt to cure hyperthyroidism in the young by medical means than it is in the adult.'

It must, however, be recognized that, despite the early dramatic results with thiouracil, the child improved after tonsillectomy. The part played by infection in the onset of thyrotoxicosis in young adults is well recognized, and Mackenzie (1931) and others have reported immediate recovery from exophthalmic goitre following the removal of very infected tonsils alone with no medical treatment.

Summary

A case of juvenile thyrotoxicosis is presented and the results of treatment with thiouracil recorded graphically over twenty-two weeks, with additional notes on progress since discharge from hospital. The possibility of its use as an alternative to surgery in the prepubertal period is suggested if similar success is met with elsewhere.

I wish to acknowledge my gratitude to Prof. Ellis for permission to publish this case and for his support and advice throughout, and to Prof. Dunlop for his opinion and advice on treatment; to Dr. W. A. Alexander for his encouragement and help; to Dr. Liebmann of the Pregnancy Diagnosis Laboratory (Edinburgh) for his investigation of the urine for follicle-stimulating hormone, and to the Biochemistry Laboratory of the Royal Hospital for Sick Children for many routine investigations.

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ACUTE NEUROTIC BREAKDOWN IN CHILDREN WITH REFUSAL TO GO TO SCHOOL

BY

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Introduction

A common problem in child psychiatry is the child who refuses to go to school, sometimes for long periods. Such children differ from those who exhibit simple truancy, and present a problem which is urgent from the point of view of both school authorities and parents.

These children always show a neurotic illness, which may involve the whole family circle. Acute anxiety is a prominent symptom, but other neurotic symptoms, obsessional or hysterical, may be found. Depression is frequent, and sexual preoccupations and fears are common. Such children often become aggressive and disobedient to their family, in contrast to their former dependent and timid behaviour. Of all their symptoms, the refusal to go to school is the most dramatic and soon becomes the focus of attention. The child clings to his home and may refuse to leave the mother: in two of the cases reported here, fears were expressed that some harm might come to the mother if the child left her. If the child is allowed to remain at home the acute symptoms tend to subside, only to reappear if any attempt is made to force him back to school: this impasse may continue for months. The mother at the same time often becomes anxious and depressed, and is soon quite unable to handle the child. To a less extent the father and siblings may become involved in what is now an acute family upheaval; this involvement of the family is important in treatment.

The whole situation springs up quite quickly and is unexpected by parents and school teachers; it may have been precipitated by a change to a new school or some such event. However, there may have been previous neurotic traits, including food fads and minor expressions of anxiety or disobedience. The subject is often an only child and is almost invariably spoilt. A neurotic and adoring mother is a common figure in the background, but the child's home and school are usually satisfactory in the material sense.

The behaviour of these children contrasts with truancy with which it is sometimes confused. These children are unadventurous, and have none of the more robust qualities, leading to active wandering from home or school, that characterize the truant; the word truant is derived with good reason from the old French term for vagrant. In these children delinquent behaviour such as stealing and lying, so common in truants, does not occur.

It was considered of interest to describe a group of such children and their treatment, in contrast with a similar group of truants who showed no neurotic breakdown.

Previous Investigations.

Partridge (1939), reviewing the subject of truancy in general, differentiated from other truants ten children that showed the symptom here discussed, but he did not consider their treatment in detail. These ten children differed from the others: they were not undisciplined; they did not dodge simple difficulties; their behaviour was not a compensation for some lack in environment; nor did they revolt against circumstances. Only one was a truant from home; on the whole they liked their schools, and yet they refused to go. Their environment showed no obvious abnormality with which their behaviour could be linked; their symptoms were due to psychoneurotic states or deviations of personality, centring round the mother in seven instances and round the siblings in two.

Johnson et al. (1941) further differentiated and developed this special type of truancy. They likewise pointed out that it was due to a psychoneurotic disorder different from the more frequent delinquent varieties of truancy, that it was associated with intense terror at being at school, and that without treatment the child would stay away from school for years.

They described eight children, four of each sex, their ages ranging from six to fourteen years. Their absence from school lasted from ten days to two years. Their intelligence varied from low average to very superior, and in most cases was superior. All the boys were submissive and obedient to their mothers, while the girls were defiant. Their past histories showed neurotic traits and anxiety. The outstanding first symptom in all cases was anxiety, and equally important was a coincident increase of anxiety in the mother, due to some simultaneously operating threat to her satisfactions, such as economic deprivation, marital unhappiness, or illness. The children still showed an undue dependence on their mothers.

As Johnson et al. held that the mother was cardinal in the causation and treatment of these symptoms, they stressed that treatment should be directed to her as well as the child, and for this reason held that two therapists were necessary. The normal practice of a psychiatric social worker interviewing the mother was insufficient, as there was need to relieve guilt and tension and for 'a positive dependent transference' on the therapist to be established. Although it was sometimes evident that neurotic symptoms in the father also contributed to the situation, it was found more practical to cope with the mother. If the child was pubescent, however, such treatment of the mother might not be necessary. They found that with these measures out-patient treatment continued for six months to a year, and as a result seven out of the eight children had gone back to school. This length of treatment and the need for two therapists stress the complexities and difficulties they encountered.

In the discussion that followed this paper Marburg described his experience with similar cases and reported a less encouraging outcome. One child he found of schizoid personality, and another developed schizophrenia later. One girl developed a manic depressive psychosis later at the age of fifteen. It is evidently necessary to follow up these cases.

Klein (1945) in a more recent paper pointed out that whatever the original causes of the refusal to go to school, secondary gains soon become prominent, obscuring the original causes and leading to a chronic state. He considered that three component motives, anxiety, aggression, and secondary gain were involved in varying proportion in the refusal to go to school, of which the latter two only were often evident to the authorities concerned, the anxiety being deep-rooted and not at first apparent. He went on to show with clinical examples that the anxiety could superficially and conveniently be separated into fear of the teacher, of other pupils, or of school work with expectation of failure. Even so the underlying causes always harked back to the family circle, for instance fear of the father might be transferred to the teacher. A boy might be over-attached to his mother, the girl to her father, or there might be rivalry among siblings. Again, secondary gains might arise from thwarting the mother, separating the parents, or defying and dominating them.

In treatment he stressed that the child must if possible be got back to school at once, even if it meant only a stay of ten minutes perhaps in the headmaster's private room. Without this contact the anxieties might not be accessible to the therapist. In his seven cases, five returned to full school life in a short time with satisfactory adjustment but two did not before the examiner realized the importance of this. In all, their speed of recovery depended on the amount of time spent on their treatment.

Present Investigation

Eight such children have been treated at the Maudsley Hospital since 1946, and the etiology, symptoms, and treatment studied in detail; they closely followed the clinical patterns described above. They were compared with a group of twelve typical truants treated during the same period. In view of the ample descriptions of truancy elsewhere, there is no need to give the case histories of the latter. There were always obvious and simple causes to be found for their truancy: these included indiscipline, some lack in the environment for which truancy was a compensation, or some reason for rebellion, for example rejection by the parents. The truants, as already stated, were free from neurotic breakdown, and they showed other delinquent symptoms.

Etiology. The ages of the children of both groups lay between nine and fourteen years, and there was little difference between them in their range of physical development, but table 1 shows the differences between them in certain respects. There was a higher proportion of boys amongst the twelve truants, hereafter called Group B, the sex ratio being 10 boys to 2 girls; in Group A the ratio was 5 boys to 3 girls. The intelligence in the eight children who had a neurotic breakdown and would not go to school (Group A) showed a high average, the range of I.Q. being 98 to 152, whereas in Group B there was a wider scatter with a proportion of the cases at lower levels, the range of I.Q. being 78 to 146.

Disturbances or lack of both maternal or paternal influence were somewhat more common in Group B although common in both groups, especially in regard to the mother. The number of only children in Group A was much higher than in Group B, and there was corresponding gross over-indulgence in the material sense.

The social environment of these children showed more detrimental factors in Group B, suggesting that material circumstances are not the main cause of such neurotic breakdown as Group A showed, though they may be of considerable importance in truancy. The assessment of progress at school again showed little trouble in Group A as compared with Group B. Only one child was being educated beyond his powers in Group A as opposed to five children in Group B.

Finally the assessment of personality showed a much higher proportion of Group A as timid, sensitive, and submissive. Every child in Group A was over-dependent on the parents, but no child in Group B was considered to be so.

Symptoms. These are shown in table 2. Neurotic traits or past symptoms of emotional disturbance, especially faddiness over food, are somewhat commoner in Group A.

With the onset of the present illness every child in Group A showed emotional disturbance in relation to his mother, sometimes with aggression, whereas in Group B fewer showed it. The contrast in neurotic symptoms was conspicuous. In Group

A 100 per cent. were acutely anxious, 50 per cent. notably depressed, 25 per cent. showed obsessional symptoms, 25 per cent. hysterical symptoms, 12·5 per cent. hypochondriacal symptoms, and 12·5 per cent. well-marked ideas of reference. In Group B 33·3 per cent. showed anxiety, and none of the other symptoms were found. On the other hand in Group B many truanted from home as well as school, or both lied and stole, whereas in Group A nothing of this occurred.

TABLE 1
ETIOLOGICAL FACTORS

	Group A Children with acute neurotic breakdown who refused to go to school		Group B Truants without neurotic breakdown	
	Number	%	Number	%
Total number of cases ..	8	—	12	—
Incidence of mental instability in near relatives	7	87·5	8	66
Emotional factors:				
Maternal attitude disturbed	7	87·5	12	100
Lack of maternal influence	1	12·5	8	66·7
Paternal attitude disturbed	4	50	9	75
Lack of paternal influence	5	62·5	9	75
Incidence of only children	4	50	2	16·7
Evidence of material spoiling	7	87·5	5	41·7
Environmental factors:				
Frequent breaks and changes in home ..	5	62·5	11	91·7
Poverty	1	12·5	4	33·3
Bad homes or neighbourhoods	1	12·5	5	41·7
Educational pressure too high	1	12·5	5	41·7
Personality:				
Timid and submissive ..	6	75	5	41·7
Over-dependent	8	100	0	0

TABLE 2
SYMPTOMS

	Group A Children with acute neurotic breakdown who refused to go to school		Group B Truants without neurotic breakdown	
	Number	%	Number	%
Total number of cases ..	8	—	12	—
Past history:				
Neurotic traits:				
Food faddiness ..	7	87·5	1	8·3
Sleep disturbances ..	3	37·5	0	0
Nocturnal enuresis ..	0	0	4	33·3
Gratification habits ..	2	25	1	8·3
Tension habits	4	50	2	16·7
Assertive habits	2	25	3	25
Present illness:				
Acute disturbance in relation to mother	8	100	7	58·3
Acute disturbance in relation to father	3	37·5	8	66·7
Acute disturbance in relation to siblings (percentage related to number having siblings, viz. 4 in Group A and 10 in Group B)	4	100	4	40
Acute disturbance in relation to school	6	75	6	50
Neurotic symptoms:				
Acute anxiety	8	100	4	33·3
Depression	4	50	0	0
Obsessional	2	25	0	0
Hysterical	2	25	0	0
Hypochondriacal	1	12·5	0	0
Ideas of reference ..	1	12·5	0	0
Delinquent symptoms:				
Disobedience	5	62·5	10	83·3
Truanting from home ..	0	0	8	66·7
Lying	0	0	6	50
Stealing	0	0	6	50

CONCLUSIONS. Children who refuse to go to school and show neurotic breakdown appear from these findings to have the following characteristics. They are mostly above average intelligence, and are timid, sensitive, and dependent. They are often only children and are almost always spoilt. Disturbances of emotional attitude in the parents, especially in the mother, are common. Unsatisfactory influences in the material environment are not important causes of the refusal to go to school.

The children studied have shown neurotic traits and particularly faddiness over food. At the onset of the present illness they all showed considerable emotional disturbance in relation to their mother, siblings, and schoolmates. They developed neurotic symptoms and especially acute anxiety, and although often disobedient and defiant they were not truants from home, nor did they lie or steal.

Treatment. Treatment of these children has been found to be difficult, prolonged, and in many ways unsatisfactory. Out-patient attendance often failed to solve the impasse that had arisen at home. Consequently three of the children were admitted to the in-patient unit at the Maudsley Hospital. This helped in their recovery, and as there is no record of such a step having been taken elsewhere, it suggests a line of treatment. Much, however, depends on the co-operation of the parents and the willingness of the child to come into hospital. In two cases considerable time was saved in their treatment, and in the other child administrative delays rather than treatment led to a long stay. It may be concluded that placement in hospital or perhaps in a suitable hostel or school for maladjusted children, coincident with psychiatric treatment, will lead to a speedier solution in suitable cases. The child is saved much anxiety and misery, and psychotherapy is easier in the neutral and emotionally uncharged atmosphere away from home. Other members of the family, particularly the mother, may have shared in the anxiety and aggression at home until recriminations or inability to control the child have led to a vicious circle.

Once away from home, the child must soon go to school each day from hospital or hostel while his treatment and in most cases that of near relatives continues. The co-operation of the educational authorities is needed, but the outcome will amply repay any such concessions made and will avert an otherwise inevitable charge of culpable non-attendance at school. In our cases the educational authorities concerned were very helpful in arranging a novel regime and disposal. The steps taken and their effect will be seen in the case records as well as the effects of too early discharge home (Case 1). Once a school had agreed to accept the child, he was taken by a nurse for a preliminary interview,

and then unobtrusively escorted each day until this was considered unnecessary. Unemotional and kindly persistence in all three cases led to regular and in due course happy attendance at the school.

Two typical cases (Cases 1 and 2) are given in some detail; the other six will be described briefly, particularly in regard to treatment and disposal. The individuals comprising such a group vary from those who were fairly easily managed to an extreme case in which medical treatment could not be undertaken. As always, treatment, whatever the generalizations that can be made from a study such as this, has to be adapted to the needs of the particular case.

Case Records

Case 1. John, aged 11 years 11 months, was first examined on Jan. 20, 1947. He had become increasingly difficult to manage at home, and later had refused to attend school; he had become depressed and aggressive to his parents and sister.

He came of a healthy and stable family; the home conditions were good, but the standards somewhat rigid. His father, aged forty-six, a lorry driver of quiet and colourless personality, took rather a passive role. His mother, aged forty-two, an unintelligent woman, had little insight and became depressed and aggressive towards her son. She had previously spoilt and overprotected him. There was a younger sister, aged ten, who was physically larger than her brother.

His birth and development were normal, but weaning was long and difficult. He was somewhat faddy over his food, always more difficult than his sister, and inclined to be jealous of her. His physical health had been normal. He had done well at school and won a scholarship to a grammar school, which he entered in the autumn term of 1946. A timid boy, he disliked cruelty, avoided being hurt, and feared low-flying planes since a rocket incident in 1944. He enjoyed the scouts, reading, and stamp collecting. His manners and speech were refined. He had no deep friendships with other boys and preferred quiet pursuits at home.

In the summer of 1946 he became difficult and disobedient at home, and, entering his new school in September, he soon stated that he disliked it and he refused to go again. He complained that other boys talked about him disparagingly but could not say in what way. He became anxious and depressed, was increasingly rebellious and bad-tempered at home, and talked of suicide. He was sulky, and so aggressive to his sister that she had to be sent away. Finally his parents gave up any attempt to control him and sought medical help.

He was found to be physically healthy, tall for his age, and on the verge of puberty. He was depressed and easily wept. Although polite and amenable, he could at first give no account of his behaviour, nor his reasons for disliking school but again stated his ideas of reference. His intelligence was superior (Stanford-Binet scale I.Q.126).

It was decided to keep him under observation as an out-patient, with a psychiatric social worker to interview the mother while the doctor treated the boy. Beyond learning more details of the history and establishing some rapport, little progress was made. John became more disturbed, and after a quarrel with his mother refused to attend hospital. Admission was arranged, and on Feb. 20, 1947, the social worker had to fetch him in. He quickly settled down, and showed no abnormality apart from undue quietness. He employed himself in all group activities and appeared content. When his parents visited him he was polite but distant.

Rapport was further built up in a series of interviews with the doctor, and his difficulties in relation to his family and school, his timidity, and his upbringing were explored and discussed. His fears of school concerned the older boys and masters, although he had suffered no actual traumata there. His increased sexual urges were evident, and his ideas of reference found to be concerned with guilt over erections. Sexual education caused these worries to cease. Independence without overt rebellion was fostered.

Meanwhile his mother was treated by the psychiatric social worker, and later by the doctor as an out-patient. The extent to which she had overprotected him, for instance she still assisted at his bath, became abundantly clear. It was his refusal to accept further her attentions and affection that marked the start of his present behaviour, to which she reacted by being hurt and then antagonistic, until finally she rejected him. She was overtly depressed, anxious, and tense, but at the same time she was resistant to discussion of herself, to which her limited intelligence and ineffective personality contributed. She failed to gain insight, and efforts to explore her difficulties more deeply were defeated. However, the enlightening fact became clear that she had long been frigid with her husband; and now, with her son's antagonism to her, she realized stronger sexual desires which her husband was unable to satisfy. Advice was given to try to alleviate this, and there was considerable discussion on her relationship with her son and her management of the situation. She inevitably became antagonistic to the doctor treating her son, but because of her lack of intelligence and because her son was pubescent no deeper psychotherapy by another doctor was attempted. As her son recovered she slowly readjusted to his changed condition.

On April 2, 1947, John was discharged home as he had long shown no overt symptoms. He continued to spend his days at the hospital, and psychotherapy continued. It was arranged for him to join a new grammar school as a fresh start. His discharge was a tactical mistake as his mother had not much improved. A gradual deterioration in his behaviour occurred in relation to her, and he became tense and irritable. He liked his new school, but soon failed

to go there after developing minor hysterical symptoms to avoid it.

On May 17, 1947, he was readmitted to hospital and promptly returned to his former happy and co-operative state. Treatment again consisted of fostering further independence, and it was appreciated that long separation from his mother was necessary. A boarding school was sought, but for months there were insuperable administrative and financial difficulties in the way; to send him to live with relations was not possible.

On June 24, 1947, he was again discharged home at his own request. John had become bored with the restrictions of hospital, and no solution was apparent. It was realized that relapse was likely, and in spite of his good resolutions and self-confidence it quickly happened and he had forcibly to be removed from a bathroom in which he had locked himself.

On July 1, 1947, he was again readmitted and remained an in-patient until his final discharge on Dec. 12, 1947, broken by ten days at a scouts' camp and an interlude with scarlet fever. As a temporary measure it was arranged for him to attend a local secondary school from the hospital, where he settled without difficulty. His voice now ' broke ' and he was quickly growing and maturing, important factors in his readjustment.

His final discharge came when it was arranged for him to go to a boarding school at the council's expense. He settled well and showed no further symptoms there or at home in the holidays. He held his own in work and took an active interest in games.

This case illustrates well the etiology of the problem and the intimate reactions within the family circle. Treatment was much helped by his removal to hospital, and his prompt relapses on discharge home bear this out. The most difficult problems were schooling and disposal, and it is considered that had these been readily available six months in hospital might have been saved, although provision for him away from home would have been necessary in the holidays. In the end this was not necessary, although sending him to boarding school was considered a wise decision because of his mother's mental state.

Case 2. Sarah, aged 11 years 6 months, was first examined on June 5, 1947. For six months she had been increasingly out of hand, had latterly refused to go to school, and was anxious and depressed.

The family was stable, with no record of mental or nervous disease. Her father, a civil servant aged forty-six, was an intelligent and co-operative man who exerted throughout a steadying influence. Her mother, also forty-six, was intellectually dull and unable to manage the patient. She showed little insight and reacted to her daughter with irritability. There was an elder step-brother abroad in the forces. Their circumstances were comfortable.

Sarah was born after seven years of sterility, she developed normally and was always healthy if highly strung. There was a history of mild sleep-walking and food fads. Her mother and to a less extent her father had spoilt and overprotected her. The war years were spent in a provincial town with her family, where they had a good home and garden. She was happily settled in her school and had plenty of friends. She was considered to be a bright child, enjoying outdoor activities, somewhat selfish but at no time a source of worry. Both father and patient were aware that she was cleverer than her mother.

In December, 1946, the family moved to London to a cramped flat, where she had to share her parents' bedroom. She became unhappy, disliked her new surroundings, and urged that they go back to their previous home. She was disobedient to her mother although her relationship with her father remained a good one. She made no friends except for a more mature girl of thirteen with whom she spent much time. Attempts to get her to go to two schools ended in uproar and failure. She was anxious and depressed, slept poorly, and made hypochondriacal complaints. If left alone she was fairly happy and content.

When examined she was in good health and on the verge of puberty: her breasts were developing. She was tearful, timid, and depressed. She talked freely but without insight of her dislike of London and school and of her hypochondriacal symptoms. Her intelligence level was average (Stanford-Binet scale I.Q. 98).

She was first treated as an out-patient, and a start was made to explore the situation more deeply. The mother was also interviewed by the doctor, but her lack of intelligence made it difficult to help her. The parents were advised not to force the issue of school, but meanwhile Sarah got more out of hand and the situation deteriorated. On Aug. 18, 1947, she was admitted into hospital.

For the first three days she was mildly depressed, occasionally wept, and her appetite was poor. She complained of headaches and pains in the legs. She quickly made friends with an older girl and avoided other children. She then lost all her symptoms and became a happy co-operative child, friendly with everyone and with no desire to go home.

In therapeutic sessions before and during admission her troubles were discussed—her relationship with her mother, her home, and her school. In addition it was found that her parents went out to a pub, leaving her alone in the house, and she was very frightened by a mouse one night. They were persuaded to stop this, and a separate bedroom was arranged for her. Although this was denied, it was probable that she had witnessed or sensed parental intercourse, and her refusal to go to school may partly have been due to her desire not to leave her mother because of this. She had many dreams, which further revealed the sexual nature of her fears and phantasies. She had once been mildly assaulted by a man in a cinema who had an ' ugly face.' She described the form master in her first school in

London as having an ' ugly face.' She appeared to be preoccupied with oral and anal phantasies of birth, and with fears of menstruation. She had been told by another girl that babies came after taking a pill, and she feared that she or her mother might be poisoned. All these ceased after adequate sexual information had been given to her.

In September it was arranged that she should attend from hospital a local school, care being taken to have a mistress in charge of her class. A nurse took her at first each day. She settled happily and continued there without interruption after she left hospital. All this time her relations with her father remained good, and he was always able to reassure and manage her. With her mother she was less aggressive, and coincidently her mother became less disturbed. She was finally discharged home on Nov. 1, 1947, and continued to attend the out-patient department at progressively less frequent intervals. There was some return of her symptoms and fears, and an occasional day's schooling was missed because of some minor ache or pain. These finally ceased with further therapeutic interviews, and except for occasional quarrels between mother and daughter which the father always was able to patch up, there have been no further symptoms. In June, 1948, she began to menstruate.

This case again illustrates the etiology of the problem in a pubescent child, which was precipitated as in Case 1 by a change to a new school and in this case new surroundings. It was notable how easily she settled down and benefited from treatment in hospital. After the administrative experience of Case 1 placement in school was promptly and successfully made and much time was saved. The personality of the father and her relationship with him rendered her an easier problem than Case 1 in spite of the difficulty of treating her intellectually dull mother.

Case 3. Robert, aged 12 years 2 months, was first examined Nov. 11, 1946. He would not go to school as he feared his mother would not be there when he came home. This dated back some months, and he had also become anxious and aggressive. His father was a nervous and inadequate man while his mother was possessive and indulgent. There was one younger brother. Examination showed a pubescent boy of average intelligence (Stanford-Binet scale I.Q. 104). Little progress was made in treatment until he was admitted to hospital in April, 1947, his mother being very disturbed and equally difficult to treat. Once admitted he ran home twice and remained at first overtly anxious and depressed. He slowly settled and improved, and once again it was found that his anxiety centred round sexual matters which required elucidation. The next step was for a nurse to take him each day to a local school; he failed to stay there at first, but with persistence this difficulty was gradually overcome. He was finally discharged in July, 1947, and he became free from symptoms. His mother became readjusted and he has since grown in independence and self-reliance.

Case 4. George, aged 12 years 7 months, was first examined on July 24, 1947. An overmothered boy with elderly parents and three grown-up siblings, he had always been timid, with phobias and fads over food. He was happy at his school until he won a scholarship to a grammar school, which he joined in September, 1946. He was unable to keep up with the work, greatly feared the gymnasium, and finally, after a minor incident there in which he was ridiculed, he refused to go any more. He became depressed, anxious, and lost weight, and his parents were unable to cope with him. Examination showed that his intelligence (Stanford-Binet scale I.Q. 111) and personality were not up to a grammar school and it was decided to move him to a modern secondary school. He was treated as an out-patient, and settled down fairly well in this less robust environment, but he remained timid and dependent. His mother again showed little insight, and was not easy to treat, and the outlook for his future self-dependence and stability appears to be poor.

In contrast to the first three children this represents a less severe instance where there was no overt rebellion. He subsided into his previous dependent state as soon as the stress of the grammar school had been removed. Admission to hospital was not necessary.

Case 5. Daphne, aged 9 years 4 months, was first examined on Jan. 29, 1948. An over-indulged only child, she had long shown neurotic traits. Her mother was a reserved, reticent, and rather suspicious woman, while her father was a heavy drinker who had deserted the mother a few months before. Daphne had shared her mother's bed since the father's unfaithfulness, and after his departure she became irritable and anxious and refused to attend school. She would not leave her mother and screamed if any coercion was used. Examination showed an overdressed girl, precocious in manner with marked histrionic traits: her intelligence was high (Stanford-Binet scale I.Q. 152). She was easily persuaded to go back to school, and out-patient treatment has continued to mother and daughter.

This child differed from the others in that she was younger but of high intelligence. The precipitating cause was a severe one, and the refusal to go to school was easily overcome so that again admission was not necessary. There were none of the adolescent traits of rebellion against parents or preoccupation with sexual matters to be seen in the more severe cases.

Case 6. Arthur, aged 14 years 4 months, was first examined on Dec. 10, 1947. This case, and Cases 7 and 8, are examples of increasing severity in which admission to hospital has not been possible. In the first two a charge for non-attendance at school has not been incurred as they are under treatment.

Arthur was over-indulged by his mother, while his father remained indifferent and little at home. He had had many neurotic traits, and due to the war several changes of home and school. Latterly he had become miserable; he said the boys at school jeered at him and he refused to go there any more. Examination showed normal pubertal development, and his intelligence was high (Stanford-Binet scale I.Q. 126). Treatment as an out-patient has in five months failed to alleviate the situation; and his mother, also emotionally disturbed, has been unable to get him to keep more than three appointments in all. It would seem that the only way to overcome this impasse is to admit him to hospital, but to this his mother has not yet consented.

Case 7. Mary, aged 14 years, was first examined on Jan. 1, 1948. This girl's parents had an unhappy marriage relationship and she had been sharing her mother's bed to keep the father out. Her father was said to be uninterested and difficult, while her mother showed overt anxiety and was under treatment by her private doctor. Mary had long shown neurotic traits, and with puberty and the onset of menstruation she became anxious and difficult to manage. She had refused medical examination at school and later ceased altogether to go there. She would not come to hospital, and finally only came with the bait of a dog with which to play. She would not co-operate in any examination, and no progress has been made with mother or daughter in six months' spasmodic attendance. It would seem that the best chance to alter this state of affairs would be to admit her to hospital, but this could not be done against the wishes of mother and daughter.

Case 8. Henry, aged 14 years 6 months, was first examined on Jan. 20, 1948. This boy represents the extreme where no medical treatment was possible. He was illegitimate, and his mother had died. He was brought up by three aunts and two women cousins who were responsible for him. He had been completely indulged and had shown minor tension habits and nervous traits. Although essentially timid, he had gradually become aggressive to them and uncontrollable; and having established a reign of terror in the house he had for a month refused to go to school. Finally in an outburst he broke up things in the house, and with the aid of the police had to be admitted to an observation ward. Examination showed him to be normally developed for his age, but with a cleft palate. There was some emotional disturbance. He refused to attend hospital. No further investigation was possible and it was necessary for the authorities to charge him with non-attendance at school. His guardians had refused to charge him as being beyond control. He was finally sent to an approved school.

Conclusions of Treatment

Although out-patient treatment was sufficient in two instances, admission into hospital helped to make recovery relatively quick and easy. Two further children whose admission was not feasible have failed at the time of writing to improve. The last case was notable in that delinquent and aggressive trends were more definite than in the others so that the child had to be charged and sent to an approved school.

A quicker return to school, as advocated by Klein, proved valuable when the child was admitted to hospital. Out of hospital such a step obviously depends on the parents' influence over the child, which was slight or ineffective in all these cases; no independent person from the hospital was available to escort the child each day from home to school.

It was not found expedient to get a second psychotherapist to treat the mother as Johnson advised. All but one of the children were at puberty or adolescent, so that the aim of therapy was to make them self-reliant. Their mothers from lack of intelligence or unwillingness to co-operate were in varying degree difficult subjects for psychotherapy, and in practice these women's anxiety settled down as the child improved.

Antagonism between the mother and the doctor who was treating the child occurred in some cases, and was circumvented with the help of a psychiatric social worker. Rapport between doctor and child might be hard to establish because the doctor was simultaneously treating the mother, but in practice it did not cause any trouble.

Summary

The child with an acute neurotic breakdown who persistently refuses to go to school is described, and the condition distinguished from truancy. Eight cases are outlined, and their etiology and symptoms contrasted with a group of truants without neurotic breakdown. The differences between these two groups are found to be considerable. Treatment is considered in detail and its difficulties are discussed; the advantage of admission to hospital, from which a return to school could be made is emphasized.

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ERYTHEMA NODOSUM IN CHILDREN FOLLOWING ADMINISTRATION OF SULPHATHIAZOLE

BY

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The occurrence after the administration of sulphathiazole of a rash similar to erythema nodosum (sulphathiazole erythema nodosum) has been reported frequently since the introduction of this sulphonamide compound. In the first reports (Carey, 1940; Long et al., 1940; Havilland and Long, 1940; Berglund and Frisk, 1941) this rash did not receive any special attention, being regarded with many other rashes as evidence of sensitivity to sulphonamides. Gsell (1940) was the first to suspect that this eruption did not depend on the toxic effect of the drug only, but that changes in the body due to the infection for which sulphathiazole was given were also responsible.

Wissler (1942) reported briefly on nineteen children with sulphathiazole erythema nodosum and drew attention to its varying incidence during the treatment of different infections; fifteen of these children had a positive Pirquet test.

Jersild and Iversen (1942) presented nine cases, none of which had an active tuberculous infection, and reported on the histological changes in an excised lesion which they found similar to those previously described in erythema nodosum.

Miescher (1943) was the first to attempt a thorough clinical and histological study of this manifestation. He rejected the possibility of sulphathiazole erythema nodosum being a common drug rash, and he put forward the hypothesis that this eruption is the result of action of bacterial substances of an allergenic or toxic nature.

Rollof (1945), giving sulphathiazole to children with a primary tuberculous infection during the active stage and later, found that the sooner after the infection the sulphathiazole was given, the more likely was sulphathiazole erythema nodosum to be provoked. All five children who received sulphathiazole during their initial fever developed erythema nodosum. Marie et al. (1945) reported on twelve children with sulphathiazole erythema nodosum, five of whom were tuberculin-negative, and they discussed various possible theories to explain this phenomenon. Amongst these was the theory that erythema nodosum might be due to a virus and that sulphathiazole might act by activation of this virus.

Loefgren (1944a, 1944b, 1945a, and 1945b) was responsible for the most carefully studied series of sulphathiazole erythema nodosum in adults so far reported, and he concluded that this eruption is not an ordinary drug rash, but is similar in nature to the usual erythema nodosum, the sulphathiazole being a provocative factor only.

The present investigation confirms Loefgren's general conclusions but is presented because the material consists of children only, and because in some respects a different method of approach has been used and some further points have been made clear.

Material

The material for this investigation consists of (a) seventeen children in whom a course of sulphathiazole preceded the first appearance of a skin rash similar to erythema nodosum (Group A, table 1), (b) thirty-two children in whom sulphathiazole was given for therapeutic or experimental purposes at varying intervals after an eruption of erythema nodosum. Twelve responded with an eruption of lesions similar to erythema nodosum (Group B, table 2) and twenty did not (Group C, table 3). In addition the case histories of other eighteen children with erythema nodosum and of all children who were treated with one or more courses of sulphathiazole for various infections in this department were studied.

Possibility of Coincidence

Before an attempt is made to explain the nature of this eruption, the question arises whether the occurrence of erythema nodosum following the administration of sulphathiazole is not a simple coincidence.

Were the occurrence of erythema nodosum after the administration of sulphathiazole a simple coincidence, the eruption should appear in a similar proportion of patients receiving other sulphonamide drugs; yet the numerous published reports of erythema nodosum following sulphonamide therapy include only three cases in which the drug was not

TABLE 1
SULPHATHIAZOLE ADMINISTRATION BEFORE THE FIRST ERUPTION OF ERYTHEMA NODOSUM

Case	Age	Sex	Reason for sulphathiazole administration*	Amount taken until eruption (g.)	Days until eruption†	Mantoux	X-ray findings	Duration of skin lesions (days)	Remarks
W.McK.	10	M.	Abd. pain thought to be peritonitis	10	3	0·01 mg. O.T. positive	Enlarged L. hilum + extension to L. middle zone	4	
R.B.	10	M.	Abscess of calf and inguinal adenitis	17	2½	0·01 mg. O.T. positive	Nil	4	
J.M.	4	F.	Abscess of neck	12 and 14 (2 courses)	13 4	0·01 mg. O.T. positive	Nil	6	Biopsy from gland of neck after incision showed T.B. granulation tissue.
J.L.	2	F.	Symptoms from respiratory system	4-5	9	0·1 mg. O.T. positive	Enlarged L. hilum	Not accurately known	Died 3 months later from Tb. meningitis.
P.S.	5	M.	Tb. meningitis. Sulphathiazole given to study possible renal lesions	44	11	0·01 mg. O.T. positive	Some peribronchial thickening	2	Died 2 days after eruption. Lesions faded during few hours before death. Mantoux after eruption negative to 0·01, positive to 0·1 mg. O.T.
A.L.	6	F.	Ruptured appendicitis and local peritonitis	9	2	0·1 mg. O.T. positive	Enlarged R. hilum. Pleurisy R. horizontal fissure	3	Developed parenchymatous lesion R. upper lobe, which resolved after one year.
S.S.	8	F.	Sore throat	10 (in 2 days)	9 (last 7 days no sulphathiazole)	0·005 mg. O.T. positive	Enlarged R. hilum and probable thickening interlobar fissure	15	The small amount of sulphathiazole the long incubation period, and the long duration of the rash make possible that in this case genuine E.N. would have appeared without provocation by the drug.
E.H.	15	F.	Symptoms of acute respiratory illness diagnosed as pneumonia	18	1½	1 mg. O.T. positive	Many ill-defined patches in upper and middle zones	8	No changes in x-ray findings after a year.
N.H.	11	F.	Febrile illness	6-12	1-2	0·1 mg. O.T. positive	Parahilar parenchymatous changes	2	
R.McF.	11	M.	Febrile illness	6	2	0·1 mg. O.T. positive	Suspicion of basal infiltration, miliary type	2	
D.C.	1 10/12	F.	Abscess of buttock	1-2	2	0·01 mg. O.T. positive	Nil	8	
A.H.	13½	M.	Febrile illness with pain in chest	9	6	0·01 mg. O.T. positive	R. pleural effusion	Less than 9	
D.H.	2 10/12	F.	Abscess of neck	12·5	5	0·01 mg. O.T. positive	Nil	3	
W.McQ.	11	M.	Acute respiratory illness	7	4	0·1 mg. O.T. positive	No evidence of primary T.B. infection	3	
J.W.	1 8/12	M.	Cervical adenitis	3	2	10 mg. O.T. negative	Nil	5	
E.M.	9	F.	Sore throat	6	2	1 mg. O.T. negative	Nil	3	
M.G.	4	F.	Cellulitis of foot	3	1	1 mg. O.T. negative	Nil	5	

* The initial diagnosis is given, although it might not have been the correct one. In twelve cases the sulphathiazole was given by the family doctor and in five while the children were treated as in-patients.
† From the first day of the administration of sulphathiazole.

TABLE 2

SULPHATHIAZOLE ADMINISTRATION AFTER A SPONTANEOUS ERUPTION OF ERYTHEMA NODOSUM : PROVOCATION OF NEW CROP

Case	Age	Sex	Interval between spontaneous E.N. and beginning of sulphathiazole administration (days)*	Amount given till eruption (g.)	Days till eruption†	Duration of skin lesions (days)	Remarks.
J.R.	6	M.	120 8‡ 5‡ 4‡ 200‡	14 6 1 18 24	3 1 One dose 3 6	3 3 No effect 2 No effect	Sulphathiazole was originally given for symptoms from the chest, due to a pleural effusion. Subsequent administrations made for experimental purposes.
S.R.	10	F.	90	9	3	2	Tuberculin negative. Etiology of genuine eruption not clear. Family history of E.N. and erythema multiforme.
W.P.	12	M.	4	9	3	2	
E.B.	13	F.	9	11	2	8–16	
E.T.	12	F.	5	18	4	3	
D.I.	10	F.	6	3	½	15	
E.W.	15	F.	10	16	4	1	
F.B.	9	M.	4	6	2	6	
N.J.	13	M.	12 7‡	4 4	1 1	5 4	Phlyctenular conjunctivitis appeared during second provocation.
S.W.	8	F.	22	10	2	6	
B.R.	3	M.	330	6	3	6	More details about this case given in text.
E.D.	13	F.	13	12	2	10	

* From the day of the eruption of the last lesion.
† From onset of administration of sulphathiazole.
‡ After the preceding eruption.

sulphathiazole (one after sulphanilamide: Loveman and Simon (1940) and two after sulphapyridine : Loefgren (1945a)). Similarly, while five out of five hundred children treated with sulphathiazole in the wards of this department since 1943 developed erythema nodosum, this manifestation was not once seen in one thousand and forty children who received other sulphonamides. This difference is statistically significant (Difference = 1 per cent., Standard error = 0·436).

If no causal relationship existed between the ingestion of sulphathiazole and erythema nodosum, provocation by this drug of new crops after the original eruption would be unlikely. As can be seen from tables 2 and 3, out of twelve cases of erythema nodosum to whom sulphathiazole was given after the complete fading of the lesions but within thirteen days from the eruption of the last lesion, a new crop appeared in eight. In thirty-seven similar cases in which there was no provocation within thirteen days from the appearance of the last lesion no new crop was noticed after the fading of the original eruption. The difference between the two groups is statistically significant (Difference = 61 per cent., Standard error = 13·53).

A slight difference in the clinical course between provoked and spontaneous erythema nodosum is mentioned below. Such a difference would not be expected if the eruption were entirely independent of preceding sulphathiazole administration. Another possible explanation of this difference is offered later.

The weight of evidence is therefore that the occurrence of erythema nodosum following administration of sulphathiazole is not a coincidence.

Comparison with Typical Drug Rash

The next question which arises is whether sulphathiazole erythema nodosum is a common 'drug rash' due to allergic hypersensitivity to sulphathiazole. Miescher (1943) described as typical of drug rash the following five points which are here compared with the corresponding characteristics of the sulphathiazole erythema nodosum cases in this series.

Drug rashes are morbilliform, scarlatiniform, or urticarial, and are diffusely distributed over the trunk and extremities. Sulphathiazole erythema nodosum is nodular and localized to the anterior surface of the legs and occasionally the thighs and extensor surfaces of arms.

Group specificity is usually present in drug rash, while it is absent with sulphathiazole erythema nodosum. As already pointed out the occurrence of erythema nodosum following the administration

TABLE 3
SULPHATHIAZOLE ADMINISTRATION AFTER A SPONTANEOUS ERUPTION OF ERYTHEMA NODOSUM: FAILURE TO PROVOKE NEW CROP

Case	Age	Sex	Interval between E.N. and beginning of sulphathiazole administration (days)*
A.Y. ..	7	M.	300
M.S. ..	10	F.	270
M.R. ..	5	F.	28
M.H.†	9	F.	40
W.J. ..	12	M.	35 155
B.H. ..	11	F.	26
J.S. ..	8	F.	33
V.C. ..	11	F.	26
B.B. ..	9	F.	50
J.L. ..	9	M.	13
G.D. ..	4	M.	15
M.A. ..	12	F.	40
M.L. ..	5	F.	14
C.J. ..	14	F.	40
S.T. ..	9	F.	7
P.C. ..	8	F.	More than 20
B.S. ..	11	F.	10
E.S. ..	12	F.	More than 14
F.M. ..	10	M.	More than 6
J. Ry. ..	13	M.	90

* From the day of the eruption of the last lesion.
† Seven days after onset of sulphathiazole administration: patient had a rise of temperature and developed a generalized morbilliform drug rash.

of a sulphonamide compound other than sulphathiazole is extremely rare. In this respect it is of interest that in case J.R., sulphamezathine was given without any effect between two successful provocations of erythema nodosum by sulphathiazole.

Continuation of the medication after the eruption of a drug rash intensifies the rash and often causes stormy constitutional symptoms. In sulphathiazole erythema nodosum this does not happen. Sulphathiazole administration, continued from twelve hours to five days after the eruption in six cases of Group A and in nine of Group B, caused no difference either in the severity of constitutional symptoms, which were generally mild, or in the intensity and duration of the rash between these children and the children in whom sulphathiazole was discontinued immediately after the eruption. The lesions often began to fade while the child was still receiving sulphathiazole.

In cases of drug rash, repetition of the medication with the offending drug causes a recurrence of the rash. In seven cases of sulphathiazole erythema nodosum this sulphonamide was given again six days to several months after the first eruption. In only three cases was a new crop provoked, and as will be seen later the success of the provocation depends on some other factor or factors.

Finally drug rashes are independent of the underlying condition, that is, of the illness under treatment or of the state of allergy of the patient. The occurrence of erythema nodosum following treatment with sulphathiazole is not independent of these factors.

Of 191 tuberculin-negative and fifty-six tuberculin-positive children who received sulphathiazole for various infections and who were watched for twelve days or more after the onset of the treatment, five developed erythema nodosum unexpectedly, and all five were among the tuberculin-positive, a percentage of 8·9 (standard deviation=3·806). Rollof (1945) had already observed this predeliction of sulphathiazole erythema nodosum to develop in tuberculin-positive children. Of thirty-five children with recent primary tuberculosis who received sulphathiazole, twenty-four, or 68·6 per cent., developed erythema nodosum, while of 788 tuberculin-negative children who were treated with the same compound, only eight, or 1 per cent., developed erythema nodosum.

Another argument against sulphathiazole erythema nodosum being a drug rash is the short interval between the course of sulphathiazole and the appearance of the nodules. In fourteen children of this series the interval was six days or less, while it is usually longer in true hypersensitivity. Treatment by sulphonamides in the past and therefore possibility of previous sensitization could be excluded in nine of these fourteen children with certainty.

The findings in the present series therefore confirm Miescher's opinion that sulphathiazole erythema nodosum is not a drug rash due to the development of allergic hypersensitivity to sulphathiazole. However, as all the above-mentioned differences between drug rash and sulphathiazole erythema nodosum are based on clinical data, a more direct approach was attempted by use of skin tests to detect hypersensitivity to sulphathiazole. The use as a testing substance of solutions of the free drug usually fails to elicit positive reactions both in typical hypersensitivity reactions to sulphonamides (references in Leftwich, 1944) and in sulphathiazole erythema nodosum (Miescher, 1943; Loefgren, 1945a). As a testing substance, therefore, serum from persons who had received sulphathiazole was used, as suggested by Leftwich (1944), with the only difference that 0·1 ml. and not 0·05 ml. of both the control and sulphathiazole-containing serum was injected intradermally; serum removed from the same person before administration of the drug was in each case used as a control. Twenty-two tests were performed on fifteen children of the present series, three of Group A, four of Group B, and eight of Group C. In addition to these, another twenty-two tests were performed on twenty-two children, seven tuberculin-negative, and

TABLE 4

SKIN TESTS FOR SENSITIVITY TO SULPHATHIAZOLE (LEFTWICH'S METHOD)

	Control cases		Cases of present series.		
	Tuberculin negative	Tuberculin positive	Group A	Group B	Group C
No difference between test-serum wheal and control	4	11	3	3	7
Test-serum wheal 1-3 mm. bigger than control	1	2	1	1	1
Control wheal 1-3 mm. bigger than test wheal	1	2	1	3	1
Test wheal 4 mm. bigger than control (considered as significant)	1				1
Total	7	15	5	7	10

fifteen tuberculin-positive controls. The results are presented in table 4.

Leftwich considered the test positive when the difference in diameter between the test and control wheal was 4 mm. or more. As can be seen from table 4, such a difference was noticed in two children only, and neither child had developed a sulphathiazole erythema nodosum. As there was no opportunity in the present investigation to try the effectiveness of the test sera on cases of typical drug rash, and the only other published work with Leftwich's method (Fink et al., 1946) throws doubts on its reliability, the results of these tests are not conclusive; but at least they do not disprove the conclusion, based on clinical data, that erythema nodosum following sulphathiazole administration is not a simple drug rash.

Nature of Sulphathiazole Erythema Nodosum

What, then, is the nature of sulphathiazole erythema nodosum? As it is not a drug rash it is natural to try to correlate it with spontaneous erythema nodosum, and a comparison between the two eruptions becomes necessary.

Clinical picture and course. On first sight sulphathiazole erythema nodosum can in no way be distinguished from true erythema nodosum. It is only by following the further development of the eruption that a slight difference becomes evident. As can be seen from table 1, in only one case was the interval between the eruption of the rash and its fading more than nine days, while among fifty cases of spontaneous erythema nodosum the rash only rarely lasted less than nine days. As appearance and evolution of lesions are otherwise the same, this difference could be considered as quantitative only, sulphathiazole erythema nodosum running a shorter course. This difference in duration has already been commented on by Miescher (1943). As the impression has been gained that the lesions of erythema nodosum fade more rapidly when the patient is at rest in bed, it is likely that this shorter duration is due, at least in part, to the fact that most of the children have been confined to bed on account of the illness for which the sulphathiazole was being administered.

Histological changes. A nodule was excised from four children with sulphathiazole erythema nodosum under general anaesthesia and in one (P.S.) after death. In three of these (R.McF., P.S., J.W.) the lesions were similar to those of erythema nodosum, and in one (A.L.) there were very mild changes; while in the last (S.S.), whose nodule was excised two weeks after fading of the lesions, the changes were compatible with the appearances in an erythema nodosum lesion of the same age. No significant difference in the histological appearances could, therefore, be detected between sulphathiazole erythema nodosum and erythema nodosum. More details about the histology of erythema nodosum and sulphathiazole erythema nodosum will be given elsewhere (Hart-Mercer and Doxiadis). Miescher reached the same conclusion although he found some quantitative differences, the lesions of sulphathiazole erythema nodosum exhibiting milder changes.

Etiology and underlying infection. Although the pathogenesis of erythema nodosum remains the subject of discussion, there is general agreement on its etiology. It is widely accepted that the eruption occurs in the course of an infective illness at a stage when allergy to the infecting agent is being established. The most common infection responsible is, in European children, primary tuberculosis, and Wallgren (1930) has shown that the appearance of the eruption usually coincides with the establishment of tuberculin sensitivity. Streptococcal infection ranks second to tuberculous as a causal agent. A survey of fifty children with erythema nodosum in the past three years confirms this view. Forty-six reacted strongly to tuberculin (0·01 mg. O.T.) and thirty-five of these had radiological evidence of primary tuberculous infection. The four who were tuberculin-negative even with large doses of tuberculin (1 to 10 mg. O.T.) had signs of other preceeding infection. Two were suffering from a pyogenic cervical adenitis following scarlet fever and tonsillitis respectively, one had acute tonsillitis, and in the fourth (S.R.) the underlying infection was unknown as the child was not seen during the original eruption. As can be seen from table 1, the seventeen children who developed sulphathiazole erythema nodosum formed a very similar group from the point of view of the underlying infection. Fourteen reacted strongly to tuberculin (0·01 to 0·1 mg. O.T.); of these, eight had radiological evidence of active tuberculous infection, one had tuberculous meningitis, and one had suppurative cervical adenitis, biopsy of which revealed tuberculous granulation tissue. Of the remaining four tuberculin-positive children in whom other evidence of active tuberculous infection was lacking, one was less than two and another less than three years old,

so it is likely that they were still in an active stage of their infection. Of the three tuberculin-negative cases (up to 1-10 mg. O.T.) one had pyogenic cervical adenitis, another acute tonsillitis, and the third cellulitis of the foot. It seems, therefore, that sulphathiazole evokes the appearance of erythema nodosum in the same phases of the same infections as in children in whom the eruption appears spontaneously. It is noteworthy that although sulphathiazole has been used extensively in the treatment of children suffering from pneumonia or meningococcal meningitis, never in this series did sulphathiazole erythema nodosum develop in such a case.

The similarity in clinical appearance, histological changes, and underlying infection between erythema nodosum and sulphathiazole erythema nodosum justifies the assumption that these two manifestations are fundamentally the same. As pointed out above, administration of sulphathiazole before the appearance of the eruption of sulphathiazole erythema nodosum is more than a simple coincidence.

In order to obtain further evidence on the relationship between erythema nodosum and sulphathiazole, observations were made on thirty-two children suffering from spontaneous erythema nodosum who were treated with the drug at varying intervals after the appearance of the initial eruption. Twelve children responded with a new crop of skin lesions. These lesions were neither as large or as indurated as the initial lesions. They tended to be localized to sites not previously affected, for example the lateral surfaces of the legs and the lower halves of anterior and lateral surfaces of the thighs, but localization on sites previously affected was also not uncommon. These lesions often faded without first turning purple.

These provoked lesions were therefore similar to those lesions of a spontaneous erythema nodosum which appear a few days after the start of the eruption and sometimes after a flare-up following a tuberculin test, and which have the characteristics mentioned above. It is only when the interval between original eruption and provocation is long that the provoked lesions have the character of the typical lesions occurring in the first few days of the spontaneous eruption, that is, the lesions are larger, more tender, and more indurated (cases J.R. and B.R.). The histology of these provoked lesions was studied in three nodules excised under general anaesthesia from two children (J.R. and W.P.). No significant difference from the histological changes in erythema nodosum could be detected in these three biopsies (see Hart-Mercer and Doxiadis).

As can be seen from tables 2 and 3, the shorter the interval between the initial eruption and the course of sulphathiazole, the more likely is provocation successful. In all but four cases with successful provocation (Group B) the sulphathiazole course began thirteen days or less after the eruption of the last skin lesion of the initial attack. In all but three cases in which provocation was unsuccessful (Group C) this interval was thirteen days or more. Of the four exceptions in Group B, the two (J.R. and B.R.) with successful provocations four and eleven months respectively after the original lesion had had at the time of provocation a reactivation or extension of their infection. J.R. developed a pleural effusion, at the first signs of which, and before the diagnosis had been established, sulphathiazole was given. B.R.'s history has some points of particular interest and it is given in more detail.

B.R. In April, 1946, at age of 2½ years, this child developed erythema nodosum. Two months later a tuberculin test was positive and radiograph of his chest showed a right hilar flare. It is fair to assume, therefore, that the erythema nodosum was a manifestation of his primary tuberculous infection. Apart from an attack of measles, and occasional attacks of bronchitis for which he was treated at home with one of the sulphonamides, probably sulphathiazole, he remained well until the beginning of December, 1946, when his cough became worse and he lost his appetite and some weight. He was admitted to hospital on Dec. 12, 1946, and at that time the chest radiograph showed extension of the opacity to the right lower lobe. Because of febrile episodes he had two courses of sulphathiazole, from Dec. 22 to 27, 1946, and from Feb. 10 to 13, 1947; he responded well on each occasion and had no skin manifestation. On March 11, 1947, his temperature rose again, but this time it was accompanied by phlyctenular conjunctivitis. He was given sulphathiazole, and three days later typical erythema nodosum appeared on both legs. A radiograph taken at that time showed a small pleural effusion which was localized anteriorly.

In this child sulphathiazole taken at various intervals after his original eruption was ineffective in provoking a new eruption. As soon as there was a reactivation of his tuberculous infection as manifested by the pleural effusion, administration of sulphathiazole provoked a new eruption of erythema nodosum.

It can very well be argued that both children were in any case going to develop a second attack of erythema nodosum, since other signs of activity of their tuberculous infection were present; but, if this were so, this spontaneous second eruption would be more likely to appear simultaneously with the other signs of reactivation, and therefore before the commencement of the administration of the drug. It is unlikely that sulphathiazole played no role, since the provocative nature of sulphathiazole has been established beyond doubt in other cases.

In all three cases of Group C in which sulphathiazole was given within thirteen days from the onset of the last lesion, the original eruption was mild and of short duration (eleven, four, and seven days respectively). It can, therefore, be assumed that in these cases the period during which sulphathiazole could still elicit a reaction ended earlier

TABLE 5

RESULT OF BIOPSY AND OF SULPHATHIAZOLE PROVOCATION ON CASES OF ERYTHEMA NODOSUM

Case	Interval between eruption and biopsy (days)	Histological changes	Result of provocation by sulphathiazole immediately after biopsy
B.H.	18	Changes of E.N.	Unsuccessful
S.W.	18	Slight changes compatible with but not specific of E.N.	Successful
S.S.	24	Slight changes compatible with but not specific of E.N.	Successful
J.W.	32	Slight changes compatible with but not specific of E.N.	Unsuccessful
M.H.	52	Negative	Unsuccessful
S.R.	90	Negative	Successful
J.Ry.	90	Negative	Unsuccessful

than in other cases with an original rash which was more marked and of longer duration.

Miescher (1943) was struck by the extent of the histological changes in nodules which were only a few hours old. He thought it likely that a flare-up was provoked by sulphathiazole in pre-existing but clinically undetected granulomatous processes. An attempt was made to clarify this point by excising under general anaesthesia a piece of skin from the exactly recorded site of a nodule at varying intervals for each case after the fading of the rash, and then giving sulphathiazole to see whether a new crop of lesions was provoked. This was done in seven cases, and the results are given in table 5. The number of observations is admittedly small, but it seems that the provocation of a new crop by sulphathiazole does not depend on the presence of persisting though clinically invisible lesions. The successful provocation in the absence of histological changes (S.R.) could perhaps be explained by assuming that the excised piece of skin did not happen to contain any of the latent lesions. But the opposite, that is, the failure to provoke a new crop although histological changes were present (B.H.), is against Miescher's hypothesis.

Conclusions

From these observations it seems that, to provoke erythema nodosum, sulphathiazole must act in the presence of infection and bacterial allergy. A first eruption following administration of sulphathiazole has always developed during the active stage of infections which are known to be present in cases of erythema nodosum even without sulphathiazole. Provocation of new lesions after an original eruption was successful only when the great degree of hypersensitivity to bacterial allergens known to exist during the appearance of erythema nodosum had not subsided below a certain level, or when sensitivity had been enhanced again by reactivation of the infection. It seems, therefore, certain that in sulphathiazole erythema nodosum the drug acts as a provocative factor only, the indispensable etiological factors being the same as in erythema nodosum.

Three possibilities may thus exist in certain infections, notably tuberculous and streptococcal, in relation to the appearance of erythema nodosum. The first in which the eruption of erythema nodosum is in any case impossible, the second in which infection alone cannot cause an erythema nodosum but in which the stimulus of a course of sulphathiazole may provoke an eruption, and the third during which infection alone can cause an erythema nodosum eruption. To which of these groups each infected organism belongs depends on many factors, the definition and investigation of which would lead into the still unsolved question of the pathogenesis of erythema nodosum in general.

The circumstances and conditions under which sulphathiazole may cause the eruption of erythema nodosum have so far been described, but the mechanism of provocation is still a matter of speculation. The first possible explanation would be that sulphathiazole by its deleterious action on bacteria liberates more bacterial antigenic substances. Against this conception is that sulphathiazole has bacteriostatic and not bactericidal properties on M. tuberculosis and other bacteria (Ballon and Guernon, 1942) and that other compounds, for example sulphadiazine, exert a stronger chemotherapeutic activity on tubercle bacilli in vivo (Smith et al., 1942), and should therefore cause erythema nodosum to a similar or greater extent. It should be borne in mind that any theory attempting to explain this mechanism of erythema nodosum provocation by sulphathiazole should also explain the peculiar position of this compound in relation to the other sulphonamides. The only property in which sulphathiazole differs from all the other commonly used sulphonamide compounds is its capacity for being bound to serum proteins much more than the others (Davis, 1943). Chemical substances acquire antigenic properties after being bound to body protein (haptens), and it is suggested that this capacity of sulphathiazole may have some connexion with its provocative power. No further explanation can be offered at the moment for the mode of action, but it is likely that further research in this direction may be fruitful.

Summary

1. Observations are recorded on seventeen children developing erythema nodosum after receiving sulphathiazole.

2. On the basis of clinical, biological, and histological data the conclusion is reached that this manifestation is not a ' drug rash ' due to allergic sensitivity to sulphonamides, but is fundamentally the same as erythema nodosum.

3. In order to elicit an eruption of erythema nodosum, sulphathiazole must be given to subjects who are in the active stage of one of the infections commonly associated with spontaneous erythema nodosum. It is therefore a provocative and not an etiological factor.

4. The mechanism of this provocation is unknown.

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THE HISTORICAL BACKGROUND OF CONVULSIONS IN CHILDHOOD

BY

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Convulsions in childhood must be as old as mankind, and it would be remarkable if so striking and terrifying an affliction had not received attention of one kind or another throughout the ages. In so far as the attitude of a community to a convulsion is merely a reflection of its attitude to medicine and an indication of its scientific and ethical background, the history of convulsions can only be in essence the history of medicine or, as we are only concerned here with children, of paediatrics. It may however be of some interest to trace briefly the evolution of the present-day conception of convulsions in childhood against the historical background.

Egypt, Babylon, and India

Although the civilizations of Egypt and Babylon, and Brahminical medicine in India appear to have had more or less enlightened views on the upbringing of children, little can be discovered of their precise attitude to convulsions. It is nevertheless likely that they all shared to some extent the view that a convulsion was due to direct divine intervention or demoniacal possession, a view that lingers even to-day in the words ' epilepsy ' and ' seizure.' In ancient Egypt this idea was carried to the extreme of holding all disease and even death to be due to the intervention of external agents (Finlayson): these agents might apparently belong to this or the ' other ' world. Thus where the intervention was not obviously of this world, such as an assassin or a falling tree, the physician had the double duty of identifying the offending spirit and thereafter of prescribing the specific treatment. Usually amulets and incantations were regarded as indispensable.

Greece and Rome

Hippocrates. European medicine begins properly in Greece. The achievements of Athens in the time of Pericles are perhaps the most astonishing in all history. Under the stimulus of victory over the Persians she produced architects, sculptors, and dramatists who remain unsurpassed to the present day. It was at this time that Hippocrates, who was thus a contemporary of Socrates and Plato, lived and taught. Born in this era of untrammelled philosophical speculation, Hippocrates' genius presents a remarkable difference from that of his illustrious contemporaries; for he was the first to treat of medicine as a practical study rather than as a speculative philosophy. His was a method of observation and inductive reasoning so ideally suited to clinical medicine. His writings deal with medicine, surgery, midwifery, embryology, climatology, dietetics, prognostics, and ethics but not specifically with paediatrics. There are, however, numerous pertinent observations in his general writings and in particular his well-known treatise on ' The Sacred Diseases,' or epilepsy. He differentiated between epilepsy and infantile convulsions but the distinction, as we might expect, is not clear.

In the ' Aphorisms ' he points out that teething is associated with a number of unhappy afflictions including diarrhoea and convulsions, this particularly at the time of the eruption of the canines and in fat constipated infants. Thus originated a belief that over two thousand years of medical progress has not quite eradicated. He also stated that those who were afflicted with the ' falling sickness ' before the age of fourteen might become free of it but those who were affected at the age of twenty-five were usually troubled with it to the end. A more important observation on infantile convulsions occurs in ' Prognostics ' (Chapter 24) and is worth quoting verbatim (Adams' translation):

' Now in children convulsions occur if there has been acute fever, and if the bowel has not been open, and if they have been sleepless, and if frightened, and if they have been screaming, and if they have changed colour acquiring a greenish or pale or livid or red colour. Convulsions occur most readily from just after birth up to the seventh year. But older children and men are no longer liable to convulsions in fevers, unless some complication with violent and very grave symptoms has arisen, as, for example, happens with acute delirium.' This it will be seen epitomizes fairly well the views on infantile convulsions held until the end of the nineteenth century.

In discussing epilepsy Hippocrates derided and rejected the view of those he termed ' the ancients ' that the condition had a supernatural cause as implied by its name. He attributed the disease rather to a specific pathology of the brain, namely, the obstruction by phlegm of the air (sic) in the

veins of the brain. He also described the aura of true epilepsy.

The importance and greatness of Hippocrates in the history of medicine lies not in the detail of his conclusions, though many of these alone would entitle him to be remembered, but in his method of clinical observation and in his insistence upon the natural origin of disease. It is one of the ironies of history that almost all that was sound in his teaching was forgotten while the dross was handed down reverently through the ages to smother independent thought.

Aristotle. Aristotle, the most versatile of all philosophers, also has a place in the history of convulsions. His father, a court physician, must have spoken often of the great physician, Hippocrates, who died when Aristotle was only fourteen. The medical writings of Aristotle, such as they are, for he was no physician, are at least reminiscent. In Book 7 (which is devoted to Man) of his treatise 'On the History of Animals' he writes:

'Children are very subject to spasms especially those that are in good condition and have abundance of rich milk, or whose nurses are fat. Wine is injurious in this complaint, and dark coloured wines more so than those that are pale . . .' He further points out that these children usually die before the seventh day and it is for this reason that the naming of the child is postponed until then.

Alexander. With Aristotle closes the period of Grecian greatness in philosophy and medicine and with his pupil, Alexander the Great, begins the Hellenistic age famed for its mathematics and science. The brief career of Alexander transformed the Grecian world. In the third century B.C. the Greek city-states came to an abrupt end with the rapid growth of the Macedonian Empire, but meanwhile the Roman Empire was beginning to take form and in the second century B.C. Greek medicine emigrated to Rome. There was no Roman tradition in medicine and indeed, before the Greek influx, Rome had 'got on for 600 years without doctors' according to the elder Pliny.

Celsus. Although medicine was practised almost exclusively by Greeks, the best account of it comes from the pen of a Roman. A. Cornelius Celsus is a subject of much controversy. He is usually said to have lived during the reign of Tiberius Caesar, step-son of Augustus, and to have been a Roman gentleman and not a physician. As to the first, Still would place him earlier, in the reign of Augustus, thus making him a contemporary of Virgil, Livy, and Horace. As to the second, this is most vehemently denied by his translator, Grieve, as also but with more evidence by Still. His are the earliest medical records extant after the Hippocratic writings, to which he shows great deference. Although he is the first to state that children should be treated entirely differently from adults, he left no paediatric writings and as regards convulsions dealt specifically only with epilepsy. His views differ little from those of Hippocrates. He emphasized that convulsions may cease at puberty, and advocated some rather startling remedies including the drinking of the blood of a newly-slain gladiator. Should these remedies be of no avail he tells us, the condition will probably last throughout life, which is not thereby shortened.

Soranus of Ephesus. Soranus of Ephesus, who lived in the second century, is the leading authority upon obstetrics and gynaecology in antiquity. He was also a paediatrician and the latter part of his work upon diseases of women is apparently devoted to infant welfare and the treatment of the commoner diseases of infancy. I have unfortunately been unable to obtain a copy of this, but in the list of contents given by Still there is no mention of convulsions or epilepsy.

Galen. The ancient period closes with the name of the greatest and most influential Greek physician. Galen, who lived from A.D. 131 to 201, founded a system of physiology, pathology and pharmacy which dominated Europe up to the time of Vesalius in the sixteenth century. At the age of 34 he settled in Rome to become court physician to Marcus Aurelius. He was a prolific writer but included little of paediatrics. In his 'De Sanitute Tuenda' he treats of infant hygiene. There is also a discourse on an epileptic boy, for whom he recommends purgation and squills together with full directions as to diet and physical exercise. In a lesser known work 'On Medical Experience' he exemplifies the importance of sequence in symptomatology thus:

'If, for example, convulsion follows fever, this is a sign of death and if fever follows convulsion, this is a sign of safety.' Galen's importance lies in the wide acceptance which his attitude of mind to natural phenomena commanded. Gone was the clinical observation of Hippocrates, gone was the imaginative freedom of thought, the heritage of the Greeks. For Galen crystallized Greek thought into a rigid system that explained everything, and the ingenuity of physicians of the next fifteen hundred years was exercised in the Procrustean task of fitting observed facts to his principles.

The Empire of Byzantium

The next six centuries saw the fall of the Western Roman Empire and the establishment of the Byzantine Empire in the east which was to last another thousand years. The degeneration of the Roman Empire into a great unwieldy administrative machine in which nearly every one of education was a civil servant gave it little strength to repel barbarians from the north. Meanwhile the Christian Church was growing rapidly into a vast and inflexible hierarchy and attracted all the outstanding minds to her service. Already torn and buffeted within by theological controversies and obsessed with the problems of heresy, she looked askance at all original thought and laid the foundations for an age of ignorance, superstition, and unspeakable cruelty which was to last over a thousand years until the renaissance. In this mental climate it would

have been extraordinary had there been any outstanding contributions to medicine. The only name of importance is that of Paul of Aegina, who lived from A.D. 625-690. He was the last of the Greek eclectics, and his emphasis that his work is not original but that of a mere scribe penning the thoughts of the masters is a sign of the times. He has nothing much to add to his predecessors; again he emphasizes the importance of dentition in convulsions, and he tends to minimize the importance of epilepsy in children. He recommends attention to diet and also the changing of a wet nurse in cases of infantile convulsions. Here he foreshadows views on the dangers of breast milk which are carried to fantastic extremes in the eighteenth century.

Islam

The Eastern Empire was also subject to repeated attacks, but while that of the west was attacked by northern barbarians who became Christians in the process, that of the east was attacked by Mohammedans who developed an important religion and culture of their own. Moreover, the religious tolerance of their régime attracted many persecuted Christians from the west, although admittedly, by the simple expedient of a tax, large numbers were enticed into the fold of Islam. The Arabian school of medicine which here grew up became the most enlightened of its time, and two Persians are noteworthy, Rhazes in the ninth century, and Avicenna in the tenth.

Rhazes. Rhazes was the first to devote an entire treatise to the diseases of children and his writings were still quoted as authoritative in the fifteenth and sixteenth centuries. A beautiful vellum-bound copy of a Latin translation of his works, printed in Venice in 1508, is to be found in the Library of the Royal Faculty of Physicians and Surgeons in Glasgow. The treatise ' De egritudinibus puerorum ' is quite short, and the chapter ' De epilepsia puerorum ' is but a paragraph of Hippocratic orthodoxy. The next chapter, also quite short, is entitled ' De quadam passione quae dicitur mater puerorum.' This is the first mention of a strange term which was later used frequently for anything from epilepsy to ' night-terrors.' In Arabian medicine it appeared to mean convulsions as opposed to epilepsy. Rhazes cites the usual causes of infantile convulsions as the cause of mater puerorum. Later it appears to mean the same as epilepsy (Mercuriale and Roelans), while later still it was used more in the sense of ' night-terrors ' in children and globus hystericus in adults. Hence ' King Lear ' (Act 2, scene 4):

> ' O ! how this mother swells up toward my heart;
> Hysterica passio ! down, thou climbing sorrow ! '

Avicenna. Avicenna, more famous as a philosopher though renowned as a physician as well, wrote largely of infant hygiene in ' Canticum de Medicina.' In ' Canonis Medicinae ' he lists the diseases of infants with little more than a statement of their occurrence, and advocates most drastic remedies such as bleeding and cupping, all directed at the unfortunate wet-nurse. He attributes the convulsions of dentition to fermentation in the gut and, of course, quotes Hippocrates.

From the Dark Ages to the Renaissance

The dark ages which followed added little to medical knowledge although the famous school of Salerno in the ninth century and that of Montpellier in the twelfth may be mentioned. It was the invention of the printing press in the middle of the fifteenth century that paved the way for the renaissance with which our modern history begins. The change in mental outlook which characterizes this period was determined by the diminishing authority of the church and the increasing authority of science. Temporal authority was now vested in the state, with a result that the culture of the period was more lay than clerical and, moreover, this lay culture was less subject to supervision and direction by the state than that of the middle ages had been by the church. The authority of science however, came much later than the rejection of the authority of the church; there was nothing scientific in the Italian renaissance. The advance of medicine therefore lagged rather behind, and it need not surprise us to find that the earlier works printed have much in common with that of the Greek eclectics and tend to be commentaries upon the Greek and Arabian schools of medicine but more enlightened commentaries perhaps. Three paediatric incunabula of this period are worth a more detailed study; the first by Paolo Bagellardus, the second by Bartholomaeus Metlinger, and the third by Cornelius Roelans. One may also mention an anonymous little book which was often quoted by Roelans and is attributed by Sudhoff to the twelfth century, named ' Diseases of Children Still in the Cradle.' This is entirely therapeutic and recommends for epilepsy peony grass and the curdled milk of a hare.

Bagellardus. Bagellardus was the author of the first printed text-book of paediatrics, entitled ' Libellus de egritunibus infantum ' and dated 1472. The first part is devoted to child care and the second to diseases, in which he treats of epilepsy and convulsions of children. On epilepsy he cites both Hippocrates and Avicenna and emphasizes its danger at an early age: ' If it happen at birth, it is not to be cured, or scarcely ever.' In nurselings the treatment is directed at the unfortunate nurse, and the list of dietary restrictions to be imposed upon her would daunt the most altruistic of souls. For older sufferers the materia medica is as picturesque as ever and ranges from the mere suspension of an emerald round the neck to the drinking of the dust (sic) of a burnt ' prickly pig.' It is hard to see in what way convulsions should differ from epilepsy, but it would seem from the short description he

gives of convulsions that these were attacks of rigidity or even opisthotonus rather than clonic convulsions. The pathogenesis is Hippocratic but the treatment dramatic. 'Yet I know from experience that I have seen many infants so stiff that they could not be bent upward or downward, who, by the mere application on the spondyles of the neck of oil of white lilies or wet hyssop, are relieved and cured by the favour of the Lord from such a contraction.'

Metlinger. The next year saw the publication of another paediatric treatise but this time in the vernacular. Metlinger wrote 'Ein Regiment der jungen Kinder' with the same respectful obeisance to the classic authorities demanded by custom but the obeisance is perhaps a little more formal and even casual. In the section devoted to disease he deals only with convulsions and although there is much of the familiar galenical therapeutics a breath of realism pervades the whole chapter. 'It should be known that when convulsions affect a child soon after birth it generally dies. My advice is to protect the children with the help of God. Children may die from this but one should protect those that come later.' 'It is advised that the nursing woman behave herself, avoid sin, avoid eating apples, be clean, and not give the child too much at a nursing but little and often.'

Roelans. Cornelius Roelans is the author of a rare incunabulum which was unknown until exhumed by Sudhoff. An almost identical text, however, was published a hundred years later by Sebastian of Austria under his own name. Roelans' book has no title page but begins with a preface in which he modestly styles himself 'aggregator' or compiler. He cites a formidable array of authorities and lists fifty-two diseases in descending order from head to foot. He also deals with both epilepsy and 'spasms.' If any authorities preponderate in his compilation it is perhaps those of the Arabian school, Avicenna and Rhazes.

The Sixteenth Century

Guillaume de Baillou. The sixteenth century is of much more interest to the paediatric historian and among a galaxy of names who contributed to the advance of medicine at that time, one, Guillaume de Baillou or Gulielmus Ballonius, wrôte on convulsions. He was the first to describe whooping-cough and the first epidemiologist of modern times. He is also author of one of the first medical dictionaries. Although he wrote towards the end of the sixteenth century, his works were published only some considerable time after his death. In 'De Convulsionibus,' written in 1587, we have the same constant reference to the ancient masters, while a combination of the view held by Hippocrates that the nasal discharge of coryza, or pituita, comes directly from the brain, with that of the cerebral origin of convulsions, leads rather interestingly to a suggestion of the pathological basis for the association of convulsions with respiratory infections.

Lesser Sixteenth-century names. Also to this period belong Sebastianus Austrius, who plagiarized the works of Cornelius Roelans, Hieronymus Mercurialis, and Scévole de Ste. Marthe. Of Sebastian of Austria, although his works were republished a hundred years later interlarded with prolix commentaries by Nicolas Fontanus and therefore presumably regarded as of some importance, little more need be said; the last word is with the masters. Mercurialis, writing towards the end of the century, shows more originality of thought but with no particular reference to convulsions. Scévole de Ste. Marthe might also be passed over but for the remarkable form in which his treatise on children, 'Paedotrophia,' was written. A Latin epic upon the care of children would seem to be in a strange medium. More remarkable still is its apparent popularity at this time. It was twice translated into English in verse. The sole contribution to the study of convulsions that he makes is the elegant presentation of an inelegant remedy, namely, the powdered ash of human skull.

Thomas Phayer. The sixteenth century also saw the publication of the first book on the diseases of children written in English. The earliest edition extant of 'The boke of children' by Thomas Phayer or Phaer is dated 1545 (the edition consulted, 1546). The fame of Thomas Phayer as a lawyer and a physician was almost eclipsed by his renown as a poet but his medical works nevertheless occupied an important place in the medical literature for the next half century. He devoted one chapter to the 'falling-evil called in the greek tongue epilepsia.' As to etiology he states that it is 'sometime by nature received of the parents, and that it is impossible or difficile to cure, sometime by evil and unwholesome diet, whereby there is engendered many cold and moist humours in the brain.' Otherwise he is largely concerned with prophylaxis and treatment. For the former he recommends as charms to be hung round the neck, 'mistletoe of the oak taken in the month of March, and the moon decreasing' and 'the stone that is found in the belly of the young swallow being the first brood of the dame.' In his therapeutics one feels that the poet has as much to say as the physician: one should give with water and honey, the 'maw of leveret,' powdered root of peony, or 'the purple violet that creepeth on the ground in gardens and is called in English, "heartsease."'

The Seventeenth Century

On the whole the sixteenth century was more occupied with theology than with science. In medicine there was little more than some crude theorizing and meagre observation. The scientific awakening that followed the religious liberation of the renaissance was largely of the seventeenth century, culminating with the publication of Newton's 'Principia' in 1687. Réné Descartes, who is regarded as the founder of modern philosophy, also contributed to modern science

and in particular to physiology. It is as a philosopher, however, that he has had most influence on medicine and science in general. His break with the scholasticism of the past and his examination de novo of the problem of existence paved the way for a rational investigation of the phenomenal world.

The great advances in every direction of human activity during the seventeenth century permit only of passing reference. The names of Kepler, Galileo, and Newton in science, Descartes, Hobbes, Spinoza, and Locke in philosophy, and Sydenham, Harvey, and Glisson in medicine are eloquent of the greatness of this period. Of those concerned with children in general and convulsions in particular, a more detailed consideration may be of interest. Nicolas Fontanus may be dismissed as belonging at heart to a former century. Similarly J. Starsmare whose 'Children's Diseases' published anonymously in 1664 contains nothing new in the conception of convulsions except an ill-defined relationship to the phases of the moon.

Robert Pemmell. Robert Pemmell, a practitioner in Cranebrook in Kent, was the author, a hundred years after Phayer, of the second book on diseases in children published in English. The full title of this book, including as it does an apologia, is worthy of reproduction. 'De Morbis Puerorum, or a Treatise of the Diseases of Children with Their Causes, Signs, Prognosticks, and Cures, for the benefit of such as do not understand the Latin Tongue, and very useful for all such as are Housekeepers and have Children.' In his chapter on 'The Falling Sickness or Convulsion' he does not differentiate between epilepsy and convulsions and lists among the possible causes, 'corruption' of the milk 'which does often happen when the nurse is of ill complexion,' also worms, smallpox, measles, or other fevers. Some cases may be hereditary or due to 'vehement pains of the teeth,' 'sudden fears,' or a thrashing. Of more interest are his comments upon phlegm (presumably upper respiratory infection) as a cause. 'Some will have phlegm to be the cause of Falling Sickness; but if it were so, then why might not old men (whose brains are phlegmatic) have the Falling Sickness . . . : Therefore the Falling Sickness doth not proceed from phlegm, but rather from an occult and sharp quality, which doth oppress the membranes of the brain. For although children do abound with phlegm (from whence suffocating rheums and other diseases be bred) yet doth not the Falling Sickness follow except there be some venomous and corrupt vapour joined therewith.'

There follow also a few pertinent remarks in the chapter upon dentition, where he quotes Hippocrates as authority for citing teething as a cause of convulsions. He reiterates the danger of this period and à propos lancing the gums he is 'confident that the want hereof doth occasion the death of many a child.'

Thomas Willis. In 1667 Thomas Willis, the celebrated author of 'Cerebri Anatome,' wrote at some length upon the subject of convulsions. Here for the first time we have a logical approach to the problem. He deals largely with epilepsy but comments that in children the term 'convulsion' is usually employed. To convulsions in childhood he devotes a separate chapter. Epilepsy may be hereditary or acquired, primary or sympathetic. It is primary when the brain is first affected and sympathetic when the brain is drawn into sympathy with other parts of the body such as the stomach, spleen, uterus, and intestines. He also differentiates between what we would term grand mal and petit mal. The immediate cause of epilepsy he gives as an 'inordinate motion of the spirits in the brain.'

He finds convulsions in children to be most common in the first month of life and during dentition. The prognosis is by far the worst in the newborn. He distinguishes two kinds of convulsion in children. The first might be called toxic, and he includes those caused by excessive heat or cold, dietary excesses, changes of air and by the sudden disappearance of an exanthem. The second might be termed reflex and he attributes these to irritation of peripheral nerves such as by milk curdled in the stomach, worms or teething. He describes in some detail how dentition causes convulsions reflexly. The growing tooth causes pressure on the fifth nerve and so presumably stimulates the brain. With regard to treatment, he advocates lancing of the gums, or 'friction' and also purging, enemata, bleeding, and vesicants. His appreciation of the value of post-mortem examination and his truly scientific approach to the interpretation of his results are a notable advance.

Walter Harris. 1689 is an important landmark in the history of paediatrics. So far there had been no generally accepted text-book of paediatrics written by a physician. Walter Harris supplied this want, and his book 'De Morbis Acutis Infantum' became the standard work on the subject and remained so, being translated into English in 1742, until the appearance of Underwood's treatise in 1789. As the relationship of teething to convulsions will play an important part in tracing the modern views on convulsions from this time onwards, it is of interest to quote Harris verbatim (Martyn's translation): 'Of all the Disorders which threaten the Lives of Infants, there is none that is wont to produce so many grievous Symptoms as a difficult and laborious Breeding of Teeth.' Apart from dentition he makes no reference to etiological factors in convulsions except one that he styles hereditary and which is apparently limited to the newborn. He attributes this to a 'Foulness contracted in the Womb.'

The Eighteenth Century

The eighteenth century which virtually begins in the final decades of the seventeenth, was a period of relief and escape; relief from the strain of a

mysterious universe. Pope's oft quoted couplet well illustrates the feeling of the times:

> 'Nature and Nature's laws lay hid in night:
> God said, Let Newton be ! and all was light ! '

To quote Basil Willey, 'Nature's laws had been explained by the New Philosophy; sanity, culture, and civilization had revived; and at last, across the gulf of the monkish and deluded past, one could salute the ancients from an eminence perhaps as lofty as their own.' The tempo of advance in science and medicine was now increasing. Observation and experiment was laying the foundation of modern medicine. One has only to mention some of the names, Linnaeus, Rutherford, Priestley, John and William Hunter, Auenbrugger, Heberden, Pott, to illustrate the greatness of this century.

Underwood. It is thus with rather a sense of disappointment that one reads the chapter on convulsions in Underwood's 'A Treatise on the Diseases of Children' published in 1789. For Underwood's text-book remained the authoritative work on the subject for over sixty years and is certainly in style and mental approach, the forerunner of the modern scientific text-book. He first describes convulsions as being of two kinds, symptomatic and idiopathic, the latter being due to a morbid affection of the brain. He doubts himself, however, the validity of this distinction and is inclined to call all convulsions, in infancy at least, symptomatic as one can usually find in every case, a cause. Of these causes the most important are teething and alimentary irritation, and he instances indigestibility of food and intestincal parasites and even 'wind' as potent causes of convulsions. In addition he attributes some cases to a dangerous quality of the breast milk which can be caused apparently by emotional changes in the mother or wet-nurse and he gives an example of a woman who had a fright and who thereupon suckled her child which straightway had a fit. For treatment he recommends purges, enemata, and bleeding.

Baumes. Another famous work is Baumes' 'Traité des Convulsions dans l'Enfance' written in 1805. He believed convulsions to be largely constitutional and attributable to 'les facheuses impressions de l'air.' The 'curdled breast milk' is given great prominence, and he instances the child of a colleague who had a convulsion after sucking at the breast of its nurse who had immediately before been very angry. The choicest anecdote is that of a woman who, knowing apparently of the dangers to her child, after having lost her temper suckled her little dog; the dog at once had a fit. All views are carried to extremes and he described convulsions of such violence as to break bones and lacerate tissues. He treats at great length of diet and hygiene as prophylactic measures. He also lists every known helminth as a cause of convulsions and would differentiate between the syndromes produced by each worm.

The Early Nineteenth Century

John Burns. John Burns included a chapter on diseases of children in his text-book of midwifery and gynaecology in 1814. He classified convulsions into those due to a primary affection of the brain, e.g. hydrocephalus, and those in which the affection of the brain is 'in sympathy' with some other organ in a state of irritation. The causes of the 'irritation' are the usual ones, and he includes Baumes' impure air. He also includes trismus of the newborn as due to constipation though he states that others believe it to be due to an infection of the umbilicus.

John Clarke. The next important contribution was that of John Clarke in 1814. His 'Commentaries on some of the most important diseases of children' contains the first clear-cut clinical description of tetany including laryngismus stridulus, carpo-pedal spasm, and convulsions. Although no etiological basis could be given for this condition, the separation of one group of convulsions on clinical grounds marked an important step in their classification. In addition there is a long chapter on infantile convulsions. He comments upon the large number of children shown as dying of convulsions in the London Bills of Mortality, but points out that terminal convulsions are not uncommon in infancy and that the probability is that a large number of deaths are so recorded whereas the underlying primary condition is not noted. Thus we have two clear-cut classes of convulsion separated from the main body, the convulsions of tetany (though not, in fact so-called until named by Corvisart) and the non-specific terminal convulsions.

John North. In 1826 John North published his 'Practical observations on the convulsions of infants.' He lists as the main causes of convulsions 'large or enlarging heads,' 'rachitis,' and 'hereditary predisposition,' and this is the first record that I have found of rickets being a cause of convulsions. However the fundamental cause is the greater sensitivity of children. This sensitivity is apparently greater in the tropics and he quotes a colleague, one Dr. Hillary, who 'observes that the children in the Isle of Barbadoes are so irritable that they are thrown into a convulsion at the slightest noise.' Loss of consciousness is not essential to the diagnosis of convulsions, which he differentiates from epilepsy in which loss of consciousness is the rule. From this he goes on to the pathological fantasy that epilepsy is derived from the brain and its membranes whereas simple convulsions come from the cord. Simple convulsions he divides into symptomatic and idiopathic though he also doubts the latter. He finds convulsions occur seldom at night, a fact that he attributes to there being fewer stimuli. He comments upon a marked increase in the incidence of convulsions and attributes it to over education. At this time children were given advanced teaching at a very much earlier age than to-day. His causes of the symptomatic convulsions are the usual ones

such as teething and constipation, though he castigates Baumes for his emphasis on helminths as a cause. He mentions, however, that in Germany the current opinion was that children rarely if ever suffered from the effects of dentition. He also describes carpo-pedal spasm as a prodromal sign of convulsions. He perpetuates the idea of harmful breast milk as a cause but the suggestion that suckling during menstruation may cause convulsions, he tells us, 'requires no further notice than the mention of its absurdity.' In addition he derides the common superstition in nurses that constipation in an infant denotes strength and advocates a purgative in all cases. He has two new etiological factors for convulsions of the newborn, retention of meconium and the shining of too bright a light on the child immediately after birth.

The Modern Period

In the next thirty years such text-books as those of Evanson and Maunsell in Dublin, and Radcliffe continue in much the same vein. Towards the end of the nineteenth century, however, the tempo of scientific advancement was accelerating to reach the breathtaking speed of the present day and the greatness of the fin-de-siècle may properly be taken as the beginning of the modern period.

Kussmaul and Tenner. In 1859 Kussmaul and Tenner described some important observations on the pathogenesis of convulsions. As a result of various animal experiments to determine the relationship between haemorrhage and convulsions, they concluded that convulsions might be produced by (1) rapid loss of blood, (2) sudden stoppage of flow of arterial blood to the brain such as produced by ligature, spasm, inflammation, or excitement, (3) rapid transformation of arterial blood to venous as in asphyxia, which, of course, would explain the association of convulsions with laryngismus stridulus. They further conclude that some cases of epilepsy may be caused in this way.

Trousseau. In 1862 Trousseau published his 'Clinique Médicale de l'Hôtel-Dieu de Paris.' Although he devotes a great deal of space to the consideration of tetany, including of course a detailed description of the sign that goes by his name, he does not relate it in any way to infantile convulsions. Indeed there is a lot that is already very familiar in his description of infantile convulsions. He classifies them as idiopathic or symptomatic, the former showing no discernible pathological change in the central nervous system except some congestion which he regards as secondary. Otherwise we have the predisposing factors of heredity, underfeeding, haemorrhage, high fever, exposure to cold or emotional upsets, and above all, local irritation including ill-fitting clothes and sinapism. The symptomatic convulsions are due either to demonstrable disease of the central nervous system or in sympathy with disease in some other part of the body such as the exanthemata.

Hughlings Jackson. The most impressive article of this period is one by Hughlings Jackson that appeared in Reynold's 'System of Medicine' in 1868. Jackson emphasises that a convulsion is a symptom and not a disease and this, though apparently simple, is a most important advance in our understanding of the problem. For consideration he divides convulsions into those affecting children up to seven years of age and those affecting children over seven.

On convulsions in the former age group he says they differ from adult convulsions only in the immaturity of the nervous system, and he considers them as equivalent to delirium in adults. He cites cerebral haemorrhage as a cause of convulsions in the newborn. He condemns the use of the terms 'essential' or 'idiopathic' convulsions or eclampsia, for he believes these convulsions to differ in no essential from epilepsy. He describes crowing and carpo-pedal spasm in convulsions but while he admits that these occur more frequently in rachitic children he includes them with other localizing indications as a manifestation of the site in the brain of the nervous discharge. Hughlings Jackson is of course responsible for the conception of epileptic discharge and that the site of maximal discharge would determine the type of manifestation at the beginning of the attack. This, as Symonds points out, was intended to apply to epilepsy as a whole and not only to traumatic epilepsy which he used however to illustrate his point. It seems particularly unfortunate that the term 'Jacksonian epilepsy' was used to denote epilepsy arising from a macroscopic pathological focus in the brain when no such restricted concept was intended by Jackson. He was concerned with the localization of the lesion and not with its pathology and would, one feels sure, have agreed that the commonest cause of a Jacksonian attack is idiopathic epilepsy. He next makes the vitally important point that such factors as over-eating, worms, and teething will not produce convulsions in a healthy nervous system. He does not try to differentiate between eclampsia (or idiopathic convulsions of childhood) and epilepsy but points out that many epileptics give a history of convulsions in childhood which had been disregarded. For treatment he condemns the routine use of purges, emetics, and lancing of gums and rather doubtfully allows their use if there is an obvious indication.

Soltmann. The experimental work of Soltmann in 1876-78 is of great importance in the study of convulsions in children. He was the first to approach the problem of the greater susceptibility of children to convulsions experimentally. He demonstrated in animals aged one to ten days, that stimulation of the cortex produced no result whereas there was hyper-excitability of the peripheral nerves. He reckoned the ten days to be the equivalent of six months in man and postulated immaturity of the nervous system with failure of the reflex inhibiting

motor centre of the brain. This was an important physiological observation but the corollary that any peripheral ' irritation ' might therefore be responsible for a convulsion seems decidedly retrograde, particularly in the light of the previous work of Hughlings Jackson. However, Soltmann's views did not pass unchallenged and Fleischmann made the pertinent observation that in burns—an especially striking form of ' peripheral irritation '—convulsions did not occur, while Henoch pointed out that the liability of children to convulsions was not limited to the first six months or even the first year of life.

Henoch. Henoch was a pupil of Schönlein and one of the principal German contributors to paediatrics. In his ' Lectures on Children's Diseases ' he discusses the pathology of convulsions in relation to the recent work of Kussmaul and Tenner and also suggests head injury as an occasional cause with extravasation of blood into the medulla. In repeated convulsions, however, he recommends examining the bones for ' according to my experience, the tendency to convulsions is favoured by nothing so strongly as rickets.' In children aged six months to three years with convulsions, rickets was usually more or less marked and laryngismus either concomitant or alternating with the convulsion, almost constant. He considers rickets to be more important than dentition in this connexion. In reflex causes he places irritation of the gut first, though he had seen no case that could be attributable to worms. In convulsions associated with a febrile illness he suggests an analogy with the rigor of an adult. In addition he points out that any fit may be the first sign of epilepsy.

Gowers. Gowers in 1893 defines epilepsy as the result of the tendency of the brain to discharge, and separates other convulsions arising from causes other than primary states of the brain, under the head of eclampsia though he specifically excludes from this the ' single fit at the onset of an acute infection or in consequence of an indigestible meal.' He attributes the special liability of children to eclampsia to the non-myelinated state of the nerve fibres and to the fact that the lower centres in childhood are further advanced than the higher controlled centres. However, he goes on to say that the next most potent cause is rickets (then of course regarded as a ' constitutional ' disease of unknown etiology) and attributes to rickets the majority of so-called teething convulsions. He notes the association of carpo-pedal spasm and laryngismus with rachitic convulsions. He accepts, however, gastro-intestinal irritation by indigestible food or worms as a cause.

Paul Simon. Paul Simon, writing in Grancher, Comby, and Marfan's text-book in 1898, also criticizes Soltmann's theory on the ground that as all children do not have convulsions though they are all exposed to some degree of the peripheral irritation that should cause them, there must be some specific predisposition. This he suggests may be hereditary or due to debility especially of the nervous system as in prematurity, artificial feeding, haemorrhage, intestinal flux, congenital syphilis, and rickets. He denies that teething is ever a cause of convulsions but cites temper at being thwarted as one.

The Beginnings of Real Inquiry into Infantile Convulsions and Epilepsy

Now for the first time there begins a real enquiry into the prognosis of infantile convulsions and their relation, if any, to epilepsy. In 1843 Rilliet and Barthez put the question without coming to any very definite conclusion. Infantile convulsions may or may not be epileptic and time alone will tell. Bouchut in 1855 believed all infantile convulsions to be incidental and with a good prognosis. So also D'Espine and Picot (1877), who denied the relation of eclampsia (or infantile convulsions) to epilepsy, terming the former ' un accident éphémère.' On the other hand Comby in 1897 and Féré in the same year called all infantile convulsions epileptic. They both stressed the importance of heredity as an etiological factor, and Comby, while accepting as precipitating factors dyspepsia, gastro-enteritis, rickets, and eruptive fevers and pneumonia, doubted the importance of dentition. In America, Walton and Carter (1891) joined the optimists and concluded that ' epileptics are at least no more likely to have had infantile convulsions and conversely a child suffering from infantile convulsions is no more likely to suffer from epilepsy in life after a period of immunity has removed the case from the class of epilepsy beginning in infancy and becoming continuous.'

Thus we come to the twentieth century and the present day, a description of which is beyond the compass of this paper. Beginning with Hochsinger, and Thiemich, with contributions from Husler, Patrick and Levy, Graham, Herlitz, Lennox, Peterman, and Thom, the study of convulsions in infancy and childhood has been established upon a logical basis, and if there are still problems to solve, at least a great deal of the ground has been cleared.

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CASE REPORTS

SCLEREMA ADIPOSUM: A CASE WITH UNUSUAL FEATURES IN AN INFANT

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This condition is not common and there is much confusion in the literature regarding the exact nomenclature of the various types of subcutaneous fat induration occurring in young infants.

Sclerema adiposum was originally described by Usembenzius (1722), and some years later Underwood (1784) reported the condition in some detail. A classical description of the types of induration occurring in the subcutaneous tissues of newborn infants was given by Ballantyne (1890). Since then, however, a number of distinct clinical and pathological conditions have been grouped under the one heading of ' sclerema neonatorum.' It has become especially difficult to differentiate between cases of sclerema adiposum and those of subcutaneous fat necrosis. Harrison and McNee (1926) described a number of cases of sclerema adiposum but did not separate cases of subcutaneous fat necrosis from those of true sclerema. Channon and Harrison (1926) investigated the chemical changes occurring in the fat in both conditions. Fox (1933) describes his cases under the name ' subcutaneous fat necrosis,' a term introduced by Fabyan (1907) and revived by Bernheim-Karrer (1922). Gray (1933), on the other hand, prefers the term sclerema adiposum when describing cases with similar clinical features to those of Fox (1933).

More recently Hughes and Hammond (1948) have reviewed the cases of sclerema adiposum occurring in the literature from Ballantyne (1890) onwards, and have added three cases of their own. They rejected all cases of subcutaneous fat necrosis and confined their survey to cases which fitted their definition of sclerema neonatorum.

The following case exhibited the clinical features and pathological changes of sclerema adiposum.

Case Report

Case history. The patient was a male infant aged 6 months at the time of admission on Dec. 24, 1947. He was the first child of healthy middle-aged parents. Born by Caesarean birth at full term, he weighed 8½ lb. Fed on National Dried Milk with adequate addition of vitamins, he thrived normally. He had not had any previous illness.

Two weeks before admission he appeared a little listless and ' off colour,' and did not use his arms or kick his legs about normally. A day or two later the mother noted some swelling of the legs, affecting first the left leg, but within two days both legs were swollen and brawny. She noticed that the skin over the swollen parts was shiny, especially over the calves, and she thought that the legs were a little painful when touched. A week before admission the arms began to show similar swelling and the swelling became generally more marked. The baby had remained fairly well and was taking his feeds normally. The bowels had opened normally. There had been no pyrexia.

Clinical examination. The patient was a fat, healthy looking, well nourished but rather pale infant of 18 lb. 6 oz., who lay quietly in bed taking an interest in his surroundings, but who appeared to resent handling. The general impression was of a healthy skin, but the legs, especially the calves, were hard, swollen, and brawny. There were also ' nobbly ' hard swellings on the thighs just above the knees, and on the buttocks and arms. These swellings were well defined and felt like fat masses. The arms were swollen from the shoulder to the wrist. This swelling was very hard, and had a well defined margin above at the shoulder, and a more noticeable one at the wrists, the latter giving the impression of a cuff. The hands and fingers were not swollen. These swellings were not tender and did not pit on firm pressure. The skin was firmly adherent to the masses and could not be wrinkled. The limbs were held stiffly and had a deep purplish colour. The hard swelling affected the outside of the limbs much more intensely, the inner aspects appeared much more normal on handling. There were firm, hard patches on both cheeks, which were due to involvement of the sucking pads; this gave the face a stiff look. The buttocks were hard and tense and beginning to ulcerate. The apparently unaffected areas were the scrotum, hands, fingers, toes, soles of the feet, back of the trunk, abdomen,

the flexures and internal aspects of the limbs and mucous membranes. There was no adenitis; the mouth and throat were normal. No abnormality was detected on examination of the chest, abdomen, or nervous system. The temperature was 99° F. on admission but otherwise remained between 98·4° and 97·6° F. until death seven days later. The white blood count was 26,000 per c.mm. of blood, polymorphs 62 per cent., lymphocytes 36 per cent., red blood count 2,560,000 per c.mm., haemoglobin 55 per cent. (Sahli). The blood chemistry showed the following figures: serum phosphatase 8 units, serum phosphorus 3·2 per cent., serum calcium 9·4 per cent., serum protein, total 5·38 per cent., albumin 3·69 per cent., globulin 1·69 per cent., blood urea-nitrogen 18 mg. per 100 c.cm., chlorides 420 mg. per 100 c.cm., cholesterol 138 mg. per 100 c.cm.

On the sixth day after admission the infant became more listless, and developed slight diarrhoea. He lost weight rapidly, and suddenly died on the eighth day of our observation.

Post-mortem report. The body was that of a fairly well developed male infant. A curious change was present in the subcutaneous fat. Large firm swellings were present over the four limbs but avoided the flexures. The cheeks were the site of a brawny swelling. In these areas the skin was tense and the underlying fatty tissue was very firm and hard. The subcutaneous tissue was freely movable on the underlying musculature. A small bed-sore was present over the buttocks. Post-mortem lividity was present over the upper trunk. No congenital abnormalities were found on external examination.

The pharynx and oesophagus were healthy. The thyroid and thymus glands showed no abnormality. The trachea and bronchi were clear and covered with a thin film of mucus. The pleura was clear and glistening and there was no free fluid in the pleural sacs. The lungs were well expanded and reddish-pink in colour. On section there was considerable congestion of both lower lobes but no inflammatory reaction had occurred and there was no pneumonia. The pericardium was normal. The heart was of normal size and shape, and the endocardium was healthy. No congenital abnormalities were present.

The peritoneal sac was healthy and the alimentary tract showed no pathological change. The liver, spleen, and kidney were normal. The suprarenal glands had a normal appearance and the pancreas appeared to be healthy. The dura mater and pia-arachnoid were healthy. The brain was well developed and rather soft, but on section no intracerebral lesion was found.

Histological report. The cutis was quite normal in appearance. The subcutaneous fatty layer was grossly thicker than normal and the fat cells were larger than usual. Their walls were not sharply defined, and they stained deeply with eosin. Running throughout the adipose tissue were intersecting bands of fibrous tissue. These trabeculae were much larger than usual and were densely infiltrated with inflammatory cells. These cells were mainly polymorphonuclear leucocytes, but lymphocytes and mononuclear macrophages were also present. Foreign-body giant-cells were not present. There was considerable endarteritis obliterans in the small vessels in the trabeculae, and these arterioles were surrounded by a dense polymorphonuclear infiltration. Special staining of the skin sections was carried out. Scharlach R stained the fat a bright red but failed to reveal any fat crystals. Nile blue sulphate failed to reveal the presence of free fatty acids, and Benda's stain showed that no necrosed fat was present. Thus only neutral fat could be demonstrated in these sections.

The skeletal muscle was completely unaffected. In the kidney the capsule, glomerular epithelium, and Bowman's capsule were normal. The convoluted tubules showed moderate cloudy swelling. The collecting tubules were healthy.

In the myocardium the fibres were pale and showed cloudy swelling. Some inflammatory cell infiltration had occurred. The cells were mainly polymorphonuclear leucocytes. The appearance was that of toxic myocarditis.

The liver capsule was normal. The liver cells were healthy and the normal lobular architecture was preserved. There was dense infiltration of polymorphonuclear leucocytes. These were present in the sinusoids and in the portal tracts. The bile-duct epithelium was healthy.

Examination of fat from the chest and abdomen failed to reveal changes similar to those found in the subcutaneous adipose tissue.

This was a case of sclerema adiposum with well marked lesions in the subcutaneous adipose tissue. There was probably a terminal septicaemia.

Comment

As Sternbach and Robinson (1947) have pointed out, the diagnosis of sclerema has not always been applied to conditions of similar etiology. As Eichenlaub and Sandler (1937) remarked, five separate clinical entities tend to be grouped under the heading 'sclerema neonatorum.' These are scleroedema, oedema, scleroderma, subcutaneous fat necrosis, and sclerema adiposum. Oedema and scleroedema show pitting on pressure and are more generalized in the early stages. Scleroderma is a condition involving the skin; the subcutaneous fatty layer is unaltered. In the present case there is clearly no involvement of the skin (fig. 2).

Subcutaneous fat necrosis may be differentiated both by the clinical and by the pathological findings. It is a less fatal disease and occurs more often over the shoulders and posterior aspect of the trunk. It exhibits less tendency to become generalized than is the case in sclerema adiposum. Calcification or cyst formation may be expected. Histologically the cellular picture is also dissimilar. The predominant cell is the lymphocyte, and a foreign-body giant-cell

reaction is not uncommon. As has been stated, however, all authors do not necessarily make the same distinction between the two diseases. Harrison and McNee (1926) described several cases of sclerema adiposum whose histological changes more closely resembled those of subcutaneous fat necrosis described by Fox (1933). More recently Zeek and Madden (1946) have described a case of sclerema adiposum where the histological appearances are of a chronic nature.

Our case presents several unusual features from both the clinical and pathological points of view. Clinically, the manifestations are strikingly similar to the majority of the cases reported as sclerema adiposum neonatorum, especially in the typical distribution of the areas in which the indurated fat lesions occur in the subcutaneous tissues, and in their firm non-pitting and non-tender character. In all previous reports the onset of the fat changes was noted early in life and usually a few days after birth, but always within the first twenty-one days of life; death followed after several weeks or months of illness. In our patient the onset was at 5½ months of age and death occurred within three weeks.

The pathological features also do not completely conform with those of other recorders. Harrison and McNee (1926), Zeek and Madden (1946), and others have described cases with a chronic inflammatory reaction in the subcutaneous fatty layers. In these cases giant-cell formation of the foreign-body type has been a prominent feature and crystals of neutral fat have been found in the affected tissue. Hughes and Hammond (1948), on the other hand, classify all such cases under the heading of subcutaneous fat necrosis. They confine their series to cases which show thickening of the connective tissue bands in the subcutaneous fatty layers as the only constant feature. In their cases cellular infiltration is absent.

In the present case, however, the findings were not completely typical of either group. Considerable thickening of the connective tissue bands had occurred, but dense cellular infiltration was also present (figs. 3 and 4). This cellular reaction was not chronic in character but was very acute. The predominant cell was the polymorphonuclear leucocyte. There were only a few lymphocytes, and no giant-cells were found. Thus the appearance was that of a lesion of an acute character, and this is in complete accord with the clinical findings. Harrison and McNee (1926) in their review postulate an infective process as the underlying causal agent in this disease. This hypothesis is an attractive one and would seem to meet this case, since there is reason to believe that there was terminal septicaemia.

A thorough bacteriological examination of an acute case of sclerema adiposum should help to clear up the obscurity surrounding the etiology of the condition.

Summary

A case of sclerema adiposum is reported. The case showed several unusual features, namely the age of onset and the acuteness of the disease process revealed by histological examination. The histological appearances would appear to indicate that an acute infective process is at work.

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FIG. 1.—Infant with sclerema

PLATE VI.

FIG. 1.—Infant with sclerema adiposum.

FIG. 2.—Section of skin overlying sclerematous tissue. The skin is quite normal in appearance. There is no oedema or inflammatory reaction. × 100.

FIG. 3.—Section showing large fat cells and a broad central trabeculum. A small vessel is present and shows endarteritis obliterans. There is considerable perivascular cellular infiltration. × 100.

FIG. 4.—Section showing a broad trabeculum in which there is heavy polymorphonuclear cell infiltration. × 400.

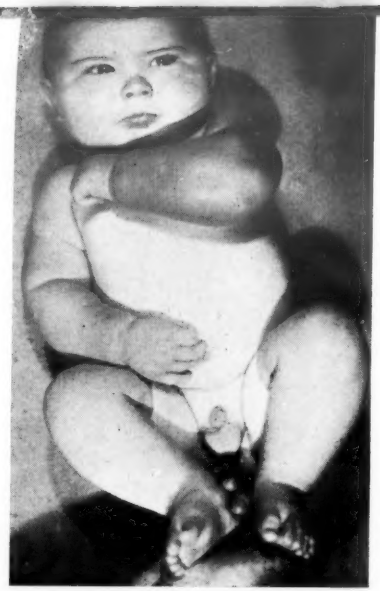

FIG. 1.

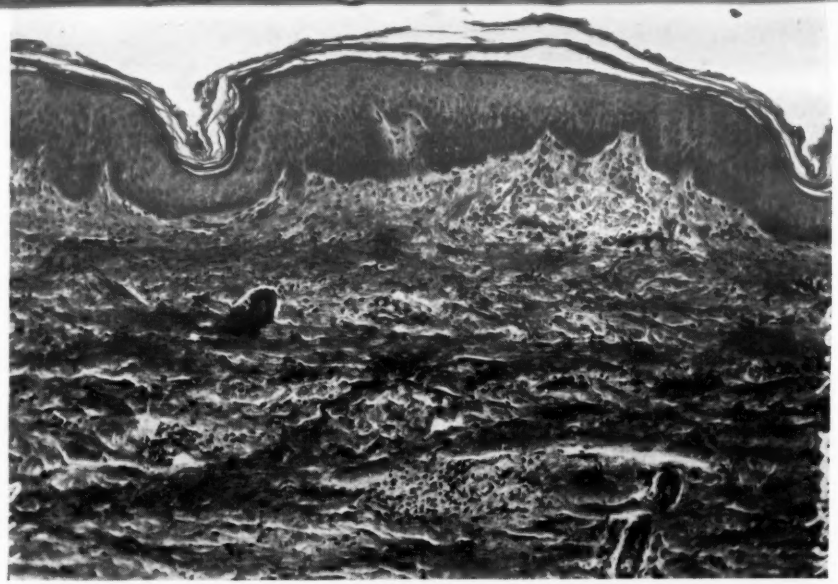

FIG. 2.

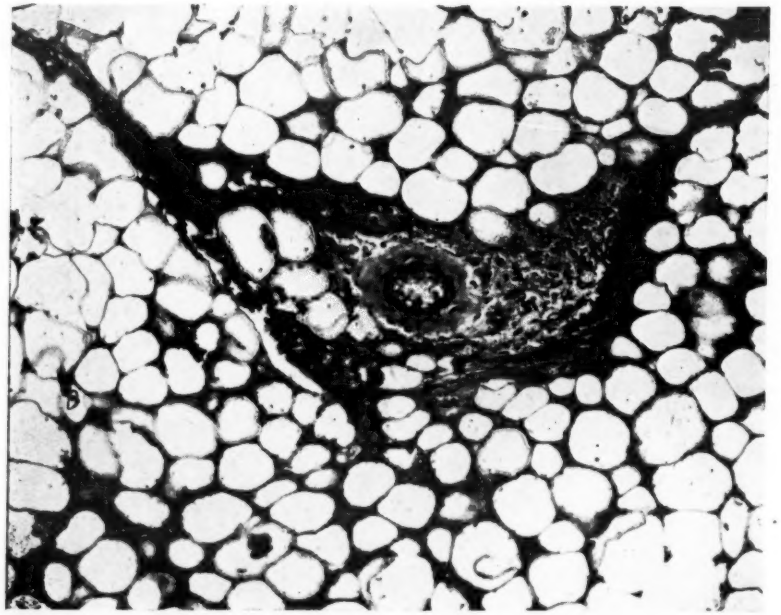

FIG. 3.

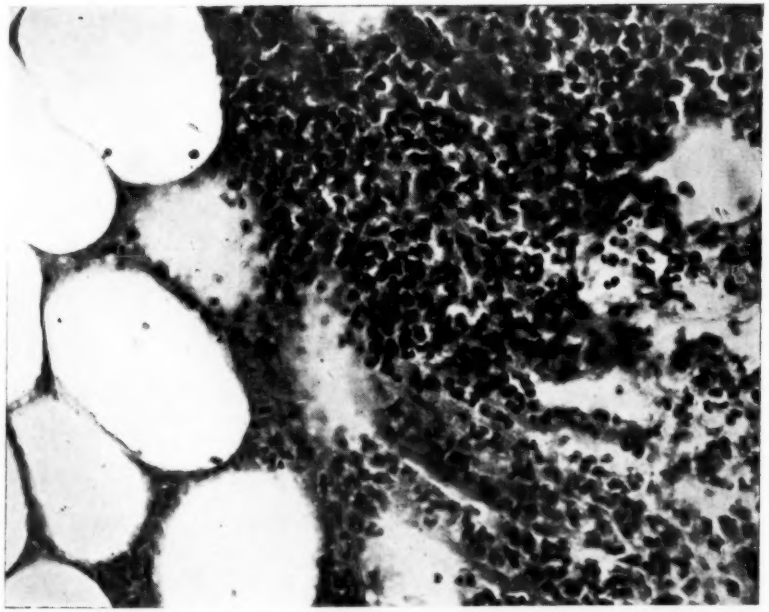

FIG. 4.

CHRONIC HYPOPLASTIC ANAEMIA ARISING IN INFANCY

BY

THOMAS ROBSON, M.D., M.R.C.P., and PATRICK J. SWEENEY, M.D., M.R.C.P., M.R.C.P.I.

(From the Royal Victoria and West Hants Hospital)

An aplasia of the erythroblastic tissue in the bone marrow, without involvement of either leucocytes or platelets, is referred to by Whitby and Britton (1946) as a medical curiosity. This aplasia may be complete or partial. If complete, there is no formation of normal red-cell precursors. Strictly speaking, the term 'aplastic anaemia' should be reserved for cases of this kind, where there is a pure red-cell anaemia without involvement of leucocytes or platelets. If the aplasia is partial, then the term 'hypoplastic' is used. 'Aleukia haemorrhagica' (Frank, 1915) would be a better term to use for conditions where red cells, leucocytes, and platelets are all reduced in numbers.

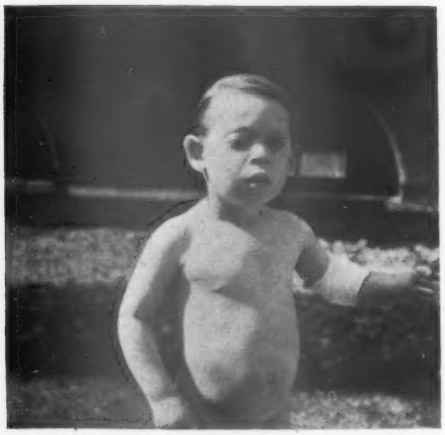

FIG. 1.—The patient.

With the more general adoption of bone-marrow biopsy as a routine haematological investigation in cases of severe anaemia, a pure red-cell anaemia may be found to be more common than is thought at present. Such cases have been described in infants, children, and adults.

Case Report

D.S., aged 1½ years, an illegitimate male child, was admitted to the Royal Victoria and West Hants Hospital on Sept. 25, 1946, with a history of having been very pale since birth. The mother had no other children, he was born of a trial labour, and weighed 6 lb. 4 oz. at birth. He had been bottle-fed from birth (National Dried Milk), and there was no history of jaundice or other infection before admission.

Examination showed a very small pale child with a slight lemon tint to the skin and moderate ptosis of the right upper eyelid which had been present since birth (fig. 1). The central nervous system was otherwise normal. No abnormality was detected in the cardiovascular or respiratory systems, and the liver and spleen were not palpable. There was no koilonychia. He was afebrile, weighing 17 lb. 5 oz., and was therefore approximately 5 lb. under weight for his age. Mentally he was backward, being unable to say words of more than one syllable. A blood count on admission showed severe anaemia (table 1) and a marrow puncture of two days later showed evidence of aplasia of the red-cell elements. A blood transfusion was given on Oct. 2 with good effect (fig. 2).

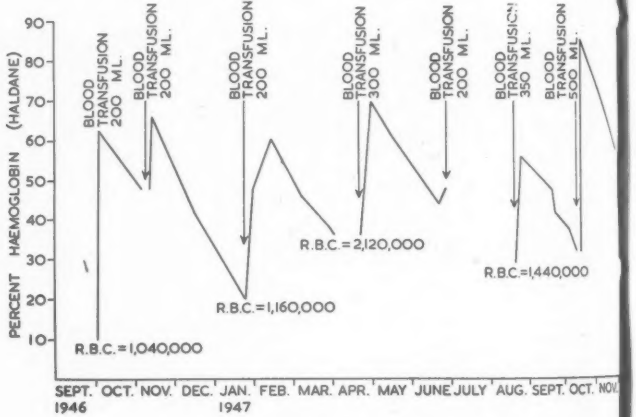

FIG. 2.—Showing per cent. haemoglobin. On Jan. 31, 1947, proteolysed liver, drachm 1, three times a day, was begun, and there was an apparent response on Feb. 14, the Hb. per cent. having risen from 48 to 60. This good effect was not maintained, however, and on Apr. 1 the Hb. per cent. was down to 36. The estimate of the Hb. per cent. was unfortunately omitted after blood transfusion of June 27, hence the gap in the chart.

From that date onward blood transfusions

TABLE 1
BLOOD EXAMINATIONS

Date	R.B.C.	Hb.%	C.I.	W.B.C.	P.	L.	M.	E.	Platelets	Retics.
26.9.46	1,230	20	0·81	12,200	23	72	3	2		
3.10.46		62								
16.10.46										0·05
6.11.46		48								
14.11.46		66								
19.12.46		42								
8.1.47		30								
24.1.47	1,160	20	0·86	9,400	37	54	8	1		
31.1.47		48								
14.2.47	3,160	60	0·95	7,200	29	64	2	5		
8.3.47	2,720	46	0·85	11,200	56	35	7	2		
29.3.47		38								
1.4.47	2,120	36	0·85	8,600	39	55	5	1		
30.4.47		70								
15.5.47	3,520	62	0·88	6,400	38	53	5	4		
21.6.47	2,360	44	0·93	12,600	39	56	5			
26.6.47		48								
7.8.47	1,440	29	1·04	8,200	47	46	2	5		
24.8.47	2,750	56							206,213	None seen
19.9.47	2,640	48	0·92	10,800	47	45	3	4		
22.9.47	2,340	42	0·91	9,100					236,000	None seen
3.10.47		38								
11.10.47		32								
15.10.47		86								
26.11.47	3,310	58	0·88	16,800	40	52	5·5	2·5		

proved the only effective treatment. At different times he was given large doses of iron and crude liver preparations, yeast, ascorbic acid, and folic acid. Iron preparations containing traces of cobalt and manganese were tried. All forms of therapy excepting blood transfusion were without much effect.

Radiographs of the skull, chest, and long bones were normal. The Wassermann reaction was negative. Both mother and child are Rh-positive, and there was no Rh-antibody in the maternal serum. Urine examination was normal. Fat analysis of the stools was within normal limits. A fractional test meal in April, 1947, showed a complete achlorhydria, but when repeated after the subcutaneous injection of histamine it showed 18 ml. N/10 acid per cent. at the end of one hour. His weight in October, 1947, was 23½ lb. He was then still five or six pounds under weight, and his height, 31½ inches, was two or three inches below the average for his age. His mental condition had improved considerably.

Repeated blood counts during the year in which he was observed constantly showed a normocytic normochromic anaemia and very low or absent reticulocytes but normal platelets and leucocytes (table 1). The bleeding time, clotting time, and clot retraction were normal and no haemorrhagic manifestations occurred. The serum bilirubin was less than 0·2 mg. per 100 ml. of blood. Marrow puncture was performed six times in all. In September, 1947, a portion of marrow from the right tibia was removed under general anaesthesia and was examined by Dr. R. G. MacFarlane, who reported on the remarkable absence of red-cell precursors and who considered an erythroblastic hypoplasia, almost amounting to an aplasia, to be well established. Details of two myelograms are given in table 2.

TABLE 2
DETAILS OF TWO MYELOGRAMS

Myelogram	1.10.46	28.8.47
Premyelocytes	3	2
Myelocytes	30	36
Eosinophils	7	1
Polymorphs	22	41
Lymphocytes	30	9
Early normoblasts	1	1
Late normoblasts	7	10

During the year the child was under observation he was remarkably free from intercurrent infections. When his haemoglobin was low he became drowsy and irritable and slight pyrexia was evident, but after a transfusion he became active and playful.

Discussion

The number of reported cases of aplasia or hypoplasia of the erythroblastic tissues alone is

very few. Lescher and Hubble (1932), in an investigation on aplastic anaemia in general, could find only three recorded adult cases. Each of these cases survived only a short time after their diagnosis, the condition appearing to have been relatively acute. Mills, however, in 1931, recorded the case of a man aged 50 years in whom the disease ran an acute course, blood transfusion being ineffective and death occurring within four months. Bone-marrow biopsy was not performed. MacFarlane and Currie (1943) described the condition in a woman aged 22 years who died after a short illness, the immediate cause of death being fatal pyrexia following the second blood transfusion. The diagnosis in this case was confirmed by marrow biopsy, which showed aplasia of the red-cell elements. Kark (1937) described two very interesting cases, the first a man of 30 years who had two hundred and ninety blood transfusions in nine years, eventually dying from a transfusion reaction. At one period this patient developed severe agranulocytosis and eventually haemochromatosis, possibly due to a failure to excrete unutilized iron. Bone-marrow biopsy was reported as showing deficient haemopoietic tissue. Kark's second case was a girl aged 21, who had sixty-one transfusions during the three years she was under observation. She finally developed thrombocytopenia and died from uncontrollable bleeding. Leslie (1945) described the case of a child who developed an apparently pure red-cell anaemia six days after birth. This child recovered after two and a half months, following blood transfusions. Marrow biopsy was not performed.

Blackfan and Diamond (1944) described five cases which seem without doubt to be true examples of pure red-cell anaemia. Of their patients, all children, two eventually recovered completely following blood transfusions, one died of pneumococcal septicaemia, and two were still under treatment at the time of publication of the paper, the eldest, aged 11, fully developed and normal in every respect, but requiring regular transfusion.

Their description of chronic hypoplastic anaemia arising in infancy, and presumably congenital in origin, is identical with that of the case recorded here. In all their cases severe normocytic normochromic anaemia developed within the first three months of life. There was no familial incidence, and no history of infection either in the patient or in the mother during gestation. There was no evidence of endocrine disturbance and little interference with growth and development; and with the exception of the one who died from pneumococcal septicaemia the children were remarkably free from infection. Blackfan and Diamond's statement that after many years' transfusions pigmentation suggestive of mild haemochromatosis develops, corresponds with Kark's experience as mentioned above.

Though in their cases the liver and spleen were not at first palpable, after some years these organs began to enlarge. The marrow showed aplasia of the red-cell elements only. Leucocytes and platelets were always normal. The bleeding times, clotting times, and clot retractions were normal. The only treatment they found effective was blood transfusion at regular intervals of six to eight weeks.

The case here recorded closely fits the above description, and is of added interest in view of the associated congenital ptosis. The ultimate outcome is uncertain, though in view of Blackfan and Diamond's report of recovery following repeated transfusions in two of their cases it appears justified to continue transfusions in the case described.

Summary

1. A case of chronic hypoplastic anaemia arising in early infancy is described.

2. From a survey of the literature it would appear that this disease can occur in infants, children, and adults, and may be acute or chronic, presumably depending upon the degree of aplasia of the red-cell elements in the bone marrow.

3. The cases arising in early infancy are probably congenital in origin, but as stated by Wintrobe (1946), there is no information about the cause of this disorder.

Our thanks are due to Dr. Facey for the numerous blood investigations, and to Dr. R. G. MacFarlane (Radcliffe Infirmary, Oxford), who examined the bone-marrow sections.

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INFECTIVE GRANULOMA OF THE GENITALS IN CHILDREN

BY

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Survey of the literature shows that there is considerable confusion about genital granulomata. Von Haam (1940) classifies them as venereal and non-venereal. Venereal granulomata may be manifestations of syphilis, gonorrhoea, chancroid, lymphogranuloma venereum, or granuloma inguinale. Non-venereal granulomata may be tuberculous, fusospirochaetal, pyogenic, or saprophytic. The last group includes those due to monilia, B. crassus of Lipschütz, trichomonas, and diphtheria.

The following cases occurring in three children living in the same house and using the same bath water presented an interesting problem in diagnosis.

Case Records

Case 1. M.D., aged 19 months (figs. 1 and 2), had on the right labium majus an abruptly projecting circumscribed oval tumour measuring 1 in. by ½ in., of firm consistency and considerable induration. When this was first seen a crust covered its surface; when the crust was removed a raw red surface was revealed. The outer border was raised and indurated. The lesion did not appear to be at all painful. The tumour had been present for one month, and there had been no previous illness.

FAMILY HISTORY. The family surroundings were healthy, but in the same house there was another small girl and also a boy aged 2½ years with similar lesions on the genitals. No rabbits or cows were kept. All the children used the same bath water.

GENERAL MEDICAL EXAMINATION. The child was well developed, intelligent, and healthy. No abnormalities were found in respiratory, cardiovascular, or central nervous systems, abdomen, or skeleton. The lymphatic glands were not enlarged, but the inguinal glands were small and shotty.

There was some redness and scaling on the forehead and chin. The general health was unaffected.

SPECIAL INVESTIGATIONS. The Frei, Mantoux, and Wassermann tests and dark-ground examination were all negative. The red cell count was 5,200,000 per c.mm. of blood and the white cell count 5,800 per c.mm. (Hb 72 per cent., polymorphs 28 per cent., lymphocytes 68 per cent., monocytes 3 per cent., eosinophils 1 per cent.).

Culture from the lesion yielded a scanty growth of micrococci only. Culture from the nearby skin yielded Strep. haemolyticus, Group G, and Staph. aureus. No pathogens were isolated from the vagina.

A radiograph of the chest was normal.

BIOPSY. In the diseased portion the epidermis was replaced by a mass of granulation tissue which extended deeply into the corium. The superficial cells of this mass were chiefly polymorphonuclear leucocytes, whereas in the deeper portion there was a dense fibrous-tissue reaction with scattered lymphocytes and occasional clusters of plasma cells.

The blood vessels appeared healthy, and there were numerous dilated capillaries in the granulomatous mass.

Sections stained by Gram's method revealed a moderate number of bacteria, chiefly Gram positive, in the superficial layers.

Giemsa and Leishman staining revealed no Leishman-Donovan bodies.

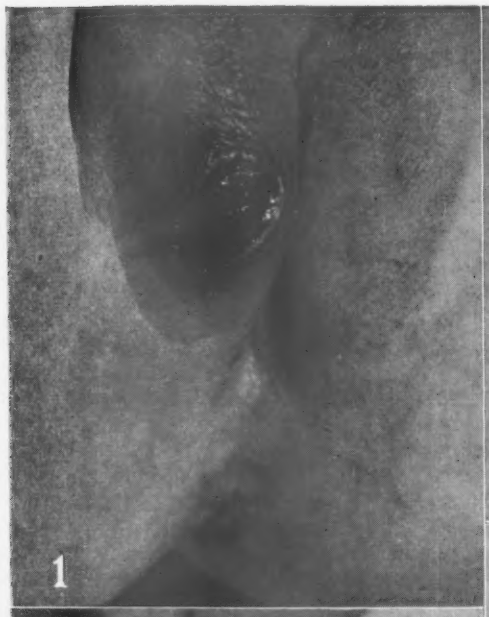
Case 2. J.V., aged 19 months (fig. 3), had a purplish-red raised circumscribed oval tumour measuring ¾ in. by ½ in. on the left labium majus, markedly projecting but with very little induration. A crust covered the surface; this, when removed, gave rise to considerable bleeding, and left a small raw area in the centre considerably smaller than the crust. The outer border was very abruptly raised. The lesion did not appear to be at all painful. It had been present for five months.

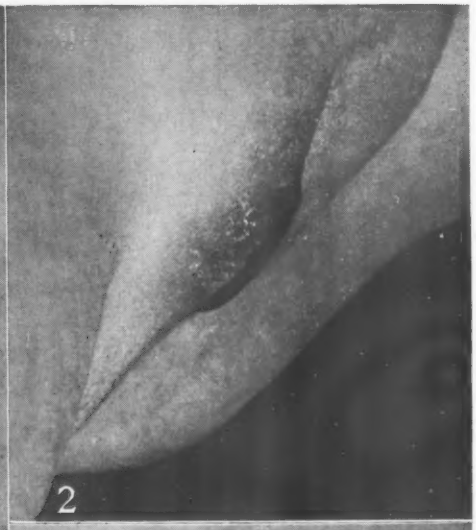
There had been vomiting and diarrhoea for one week at the age of 17 months. The child lost weight at first on artificial feeding. The birth weight was 6 lb. 13 oz.

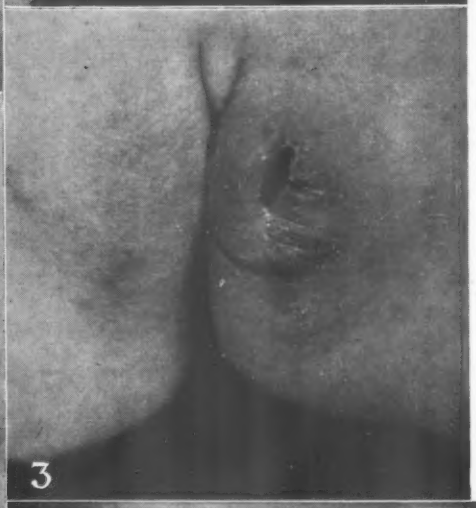
FAMILY HISTORY. An uncle had tuberculosis but had never seen the patient. The mother was a widow.

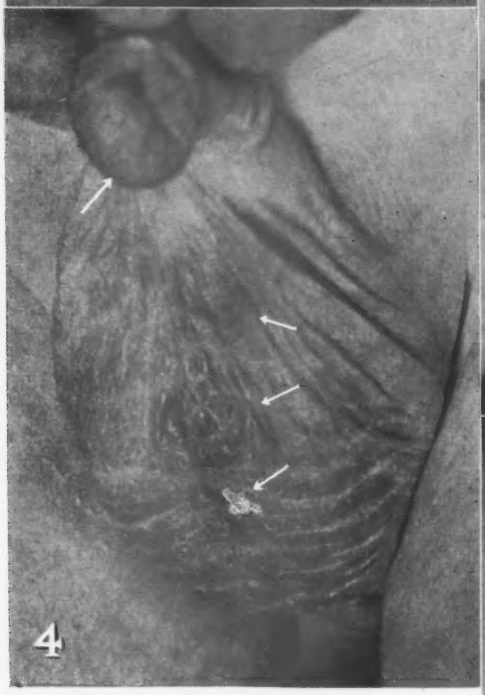
GENERAL MEDICAL EXAMINATION. The patient was a rather weakly looking child of normal intelligence. No abnormalities were found in any of the systems. The lymphatic glands were not enlarged but the inguinal glands were small and shotty. There were a very few papules and some slight erythema on both thighs. The general health was unaffected.

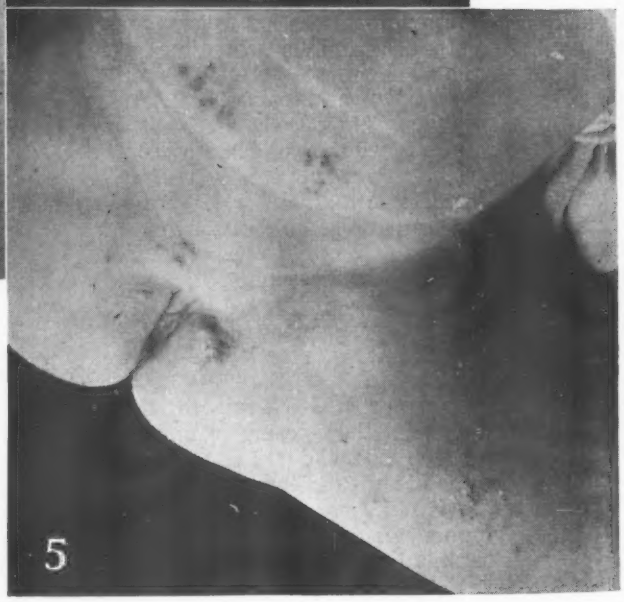
SPECIAL INVESTIGATIONS. The Frei, Mantoux, and Wassermann tests and dark-ground examination were all negative. The sedimentation rate was











FIGS. 1 and 2.—Lesion, Case 1, before removal of crust.

FIG. 3.—Lesion, Case 2, after removal of crust.

FIG. 4.—Lesions, Case 3.

FIG. 5.—Napkin rash, Case 2.

PLATE VII.

6 mm. per hour. The white cell count was 8,100 per c.mm. of blood (Hb 70 per cent., polymorphs 29 per cent., lymphocytes 67 per cent., monocytes 3 per cent., eosinophils 1 per cent.).

Culture from the lesion yielded Staph. aureus. Culture from the vagina yielded occasional Gram-negative cocci, Strep. haemolyticus group G, and micrococci.

A radiograph of the chest was normal.

The urine was acid, with a trace of albumin and occasional pus cells. Culture yielded a sparse mixed growth, probably contaminants.

BIOPSY. There was simple proliferation of the whole thickness of the epidermis in the diseased area. Beneath this there was a moderate lymphocytic and fibroblastic infiltration in the upper half of the cutis.

Giemsa and Leishman staining revealed no Leishman-Donovan bodies.

Case 3. J.W., aged 2½ years (fig. 4), on examination was found to have lesions that had almost healed and were considerably smaller than those of the other two children, but some induration was still present. There was one lesion on the prepuce and three on the median raphe of the scrotum. The condition had been present for six months and had been treated by the child's own doctor at a welfare clinic.

FAMILY HISTORY. The mother had been one year in a mental hospital and was getting a divorce from the father. It was very difficult to persuade her to show her child.

GENERAL CONDITION. The child appeared well nourished but backward, and he could not walk or talk.

CULTURE FROM LESIONS. No haemolytic streptococci, Staph. aureus, or C. diphtheria were isolated.

Discussion

In both girls the lesions clinically bore some resemblance to epitheliomata, but apart from the age of the patients the biopsy findings ruled this out. Against a syphilitic chancre was the long duration (six months in one case) and the negative serological reactions and dark-ground examination. The lesions were clinically unlike tuberculosis, and the chest radiographs and Mantoux tests were negative. Against oriental sore was the fact that the patients had never been abroad (although the fathers had served during the war in the tropics). In any case Leishman-Donovan bodies were not found. Fuso-spirochaetal lesions are invariably deep ulcers as opposed to granuloma, and moreover they are painful. No organisms of this nature were seen. Against lymphogranuloma venereum were the facts that Frei's test was negative and the inguinal glands completely unaffected. The lack of glandular enlargement, the presence of induration, and the absence of the bacilli ruled out Ducrey's infection. Again the painlessness, the age of the patients, and the long duration also ruled out the ulcus vulvae acutum of Lipschütz. Against granuloma inguinale tropicum were the facts that the patients had never been abroad and the circumscribed nature of the lesions. A Bartholin's cyst was a possibility, but no gonococci were found and Bartholin's gland does not develop before puberty. Against diphtheria was the failure to grow this organism, and the facts that both children had been immunized and that diphtheritic lesions are usually painful. Most rare conditions were ruled out by the lack of systemic disturbance.

The only remaining possibility was ecthyma, but against this was the fact that the lesions were solitary and not painful, and confined to the genitals. The medium of infection appeared to have been the bath water and towels. Possibly the fact that Streptococcus haemolyticus group G was present in two of the cases is of significance.

Sequel

In both girls healing appeared to be initiated by the biopsy and was complete in a few weeks. On discharge the parents were given Ung. hyd. ammon. dil. to apply and were told to report in three weeks. When seen at the conclusion of this period M.D.'s lesion had remained soundly healed, but J.V. had developed a typical napkin rash, or Jacquet's erythema, a strong smell of ammonia being noticed. The classical appearances so well described by Adamson (1909) were present, viz. erythema and multiple ulcerated papules of the pelvis, thighs, and lower abdomen, while the flexures remained free (fig. 5).

Conclusion

The lesions found seem to have been of the same nature as the ecthymatous lesions of Jacquet's erythema, but what is unique is the fact that they were solitary and so large, so indolent and so extraordinarily similar in the two girls. The common presence of the group G streptococcus lends support to Rosenow's theory of elective localization.

Acknowledgement is due to Dr. I. M. Scott for the report on the biopsies, to Dr. B. E. Schlesinger under whose care the second patient was admitted, and to Dr. W. N. Goldsmith for advice.

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REVIEWS

Advances in Pediatrics. Vol. 3. Edited by S. Z. LEVINE, A. M. BUTLER, L. EMMETT HOLT JR., and A. A. WEECH. 1948. New York and London: Interscience Publishers. Pp. 363. (Price 45*s.*)

This volume follows the general plan of its predecessors, and provides a series of critical reviews of special branches of paediatrics by recognized authorities. The following are dealt with: effects of birth processes and obstetric procedures upon the newborn infant (Dr. Clement A. Smith); retrolental fibroplasia (the late Dr. T. L. Terry); emotions and symptoms in paediatric practice (Dr. Milton J. E. Swan); therapeutic agents in the treatment of epileptiform seizures (Dr. W. G. Lennox); viral hepatitis (Dr. J. Stokes Jr.); abnormalities and variations of sexual development during childhood and adolescence (Dr. L. Wilkins); puberty and adolescence: psychologic considerations (Dr. H. Bruch); and the osteochondroses (Dr. B. Howorth). The field covered is so wide and varied that criticism is only possible in general terms: indeed, this book well illustrates the rapid specialization within a specialty that is taking place, and the difficulty facing the ' general paediatrician ' in attempting to keep abreast of his whole subject. The standard of all the articles is high, and there is no suggestion of the ' scissors-and-paste ' type of production that is becoming only too familiar.

Notes on Infant Feeding. By G. B. FLEMING, B.A., M.D., F.R.C.P., F.R.F.P.S., and STANLEY GRAHAM, M.D., F.R.C.P.E., F.R.F.P.S. Third Edition. 1948. Edinburgh: E. and S. Livingstone Ltd. Pp. 66. (Price 3*s.*)

There will always be a place for a concise, clearly written booklet on infant feeding, designed primarily for medical students. This one has already amply justified its existence, and it is to be hoped that the third edition will enjoy the success of its predecessors. The authors properly stress that feeds must be sufficient in quantity, and that when artificial feeds are prescribed the instructions must be clear and comprehensible to the more unintelligent mother. If the information given in these sixty-six pages is absorbed, the budding doctor should be able to advise on infant feeding with considerable confidence based on a grasp of the physiological principles involved.

The Rh Blood Groups and their Clinical Effects. By P. L. MOLLISON, A. E. MOURANT, and R. R. RACE. Med. Res. Council, Memorandum No. 19. 1948. London: H.M.S.O. Pp. 74. (Price 1*s.* 6*d.*)

This admirable summary makes readily available the essentials of recent work which has been scattered throughout the world literature. Such matters as exsanguination transfusion of infants with haemolytic disease are clearly described, and the indications discussed; these will be of particular interest to the paediatrician. Whilst the genetical basis of the Rh groups and the calculation of Rh chromosome frequencies are never likely to be supremely simple to the practising physician, he will certainly welcome the appearance of such an authoritative (and inexpensive) source of reference.

The Radiology of Bones and Joints. By JAMES BRAILSFORD, M.D., Ph.D., F.R.C.P., F.I.C.S., Director of Radiological Studies in Living Anatomy, University of Birmingham; Honorary Radiologist to the Queen Elizabeth Hospital, Birmingham, etc. Fourth Edition. 1948. London: J. and A. Churchill Ltd. Pp. 760, with 615 illustrations. (Price 63*s.*)

This encyclopaedic work passes from strength to strength, the fourth edition having been expanded and brought up to date. Many of the conditions described are of direct interest to the paediatrician, and since the author is well known as an authority on bone disease in childhood, his book is one which no paediatric library can afford to neglect. The high standard of reproduction of radiographs has been maintained.

Tuberculosis in Childhood. By DOROTHY STOPFORD PRICE, M.D., Physician, St. Ultan's Infant Hospital, Dublin, etc. Second Edition. 1948. Bristol: John Wright and Sons Ltd. Pp. 228, with illustrations. (Price 25*s.*)

Dr. Price's book, to which Mr. H. F. MacAuley contributes a chapter on tuberculous orthopaedic lesions, provides not only a useful summary of the author's own observations and experience, but also excellent reviews of the epidemiology, radiology, and types of spread. Separate chapters are devoted to tuberculosis in the adolescent and to extrapulmonary lesions. This book should be read by all who are apt to underestimate the importance of the primary lesion in childhood. The author claims a reduction of mortality in the 0- to 1-year age period from 77 to 28 per cent. in one clinic, a remarkable improvement even if allowance is made for improved ascertainment. But even the lower figure is still formidable, and the author would be the last to suggest that the problem of childhood and adolescent tuberculosis is not one of the gravest to be faced in post-war Europe. The book can be strongly recommended.

Modern Methods of Infant Management (Before, During and After Birth). By W. R. F. COLLIS, M.D., F.R.C.P., Paediatrician, Rotunda Hospital; NINIAN MC.I. FALKINER, M.D., SC.D., F.R.C.O.G., Ex-Master, Rotunda Hospital; P. C. D. MACCLANCEY, L.R.C.P. and S.I., Assistant Paediatrician, Rotunda Hospital; M. MORAN, S.R.N., Sister in charge Infants' Department, Rotunda Hospital. 1948. London: William Heinemann Medical Books. Pp. 285. (Price 17*s.* 6*d.*)

In his preface, Dr. Collis describes this as 'what the doctor should know that the nurse should know,' presented in as practicable a manner as possible. . . . 'The rules (of infant management) are exact and clear.' The book is designed to present the practices of the Rotunda Hospital, Dublin.

Section I is on antenatal care and the reception of the newborn baby. Section II describes the management and feeding of the newborn baby, and Section III details the treatment of various digestive difficulties without giving more than brief notes on the clinical pictures and no advice at all on differential diagnosis. Section IV deals with prematurity and various disorders and diseases of the neonatal period. The prematurity section is one of the better parts of the book, but it is surely bad teaching to-day to encourage anyone, let alone a nurse acting on her own initiative, to give intramuscular blood for haemorrhagic disease of the newborn. Every nurse or doctor attending newborn babies should have vitamin K or analogues for intramuscular administration, especially since there are reports of haemolytic disease in first babies of mothers who had had blood injections in their infancy.

The book is marred by four defects. It is not always easy to find what is practised or advised by the Rotunda School. For example, many of us to-day are exercised as to whether the psychiatrists (e.g. 'Problems of Early Infancy,' 1947, Josiah Macy Jr. Foundation) are right in insisting that babies should be with their mothers all the time. The problem is not mentioned. The second defect is that treatment is described without the indications being given. To say in reference to cases of gastro-enteritis, 'if necessary give castor oil' without explaining when this treatment is needed, is unwise in a book designed for nurses. Thirdly, much of the dogma handed on is without adequate foundation. Thus in Section I there is much dietetic advice, some at least of which appears to be uncritically assembled and doubtfully valid. Again, the advice against changing the napkin before feeding the baby is ill-considered, and the recommended custom of 'potting' the baby from one week old requires revaluation. It is a waste of the mother's time, for it has no value in relation to the acquisition of permanent bowel control and, before the age of six months, is of little value in saving washing.

The fourth criticism is the very cursory revision, which applies both to the text and index. Thus the calorie of dietetics is the large calorie, which raises 1 kg. of water one degree centigrade. One scoop of dried milk is not an ounce. It is surprising to learn that among the sources of vitamins in babies' diet are 'chestnut leaves, animal subs (sic) and putrefied fish meal.' More seriously, it is a pity that any paediatrician should mention one particular proprietary food without condemning the misleading statements the proprietors issue to the effect that it is not uncommon for a mother's breast milk to be plentiful but unsuitable for her child. In discussing the causes of constipation in infants, no mention is made of under-feeding, the commonest cause in London children, but 'hereditary constipation' is cited.

This lack of proportion, or lack of revision, appears in the emphasis placed on the necessity for a daily action of the bowels. In this country there is a greater need to discourage mothers and nurses from dosing their children than to encourage them to purge those happy breast-fed infants who pass a soft stool every second or third day.

The book is conveniently sized and well printed.

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